

ANNUAL REVIEW OF PHYSIOLOGY



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# ANNUAL REVIEW OF PHYSIOLOGY

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## PREFACE

Occasionally we find ourselves tempted to question the need of introducing each successive volume of the *Review* with a preface. However, even a brief period of reflection suffices to assure us that a few introductory remarks are both fitting and desirable.

First of all we have no other opportunity but this to place publicly on record our very deep appreciation of the ever friendly and cordial cooperation of those who join in the preparation of the reviews. The task they assume is onerous and extremely time consuming, but we have never had occasion for concern lest a reviewer dispose of his assignment lightly and in perfunctory fashion.

We trust that the readers of the *Reviews* are aware of the severe exigencies of space that beset the authors. In every case it has proven impossible to do justice to the number of papers calling for review. While some contributions to the literature fail to be cited because they are perhaps of insufficient substance, there are many others of excellent quality that fail to receive mention—reluctantly put aside in the hope that another reviewer may find them sufficiently germane for treatment in another chapter.

We are acutely aware, as are the reviewers and the readers of the *Review*, of the ever-narrowing confines of the world in which we can enjoy the friendly intimacies of intellectual collaboration. In many countries scholarship has ceased to be free and untrammelled, and science is denied her mission of pursuing openly and fearlessly her quest for truth. In such a world international cooperation is extremely difficult. Although we shall continue to strive for preservation of the international character of this *Review*, we trust that our readers will regard the matter as one that almost defies solution for the present.

To the George Banta Publishing Company, to our editorial assistants, and to those who have aided us with many helpful suggestions we wish to express our grateful appreciation.

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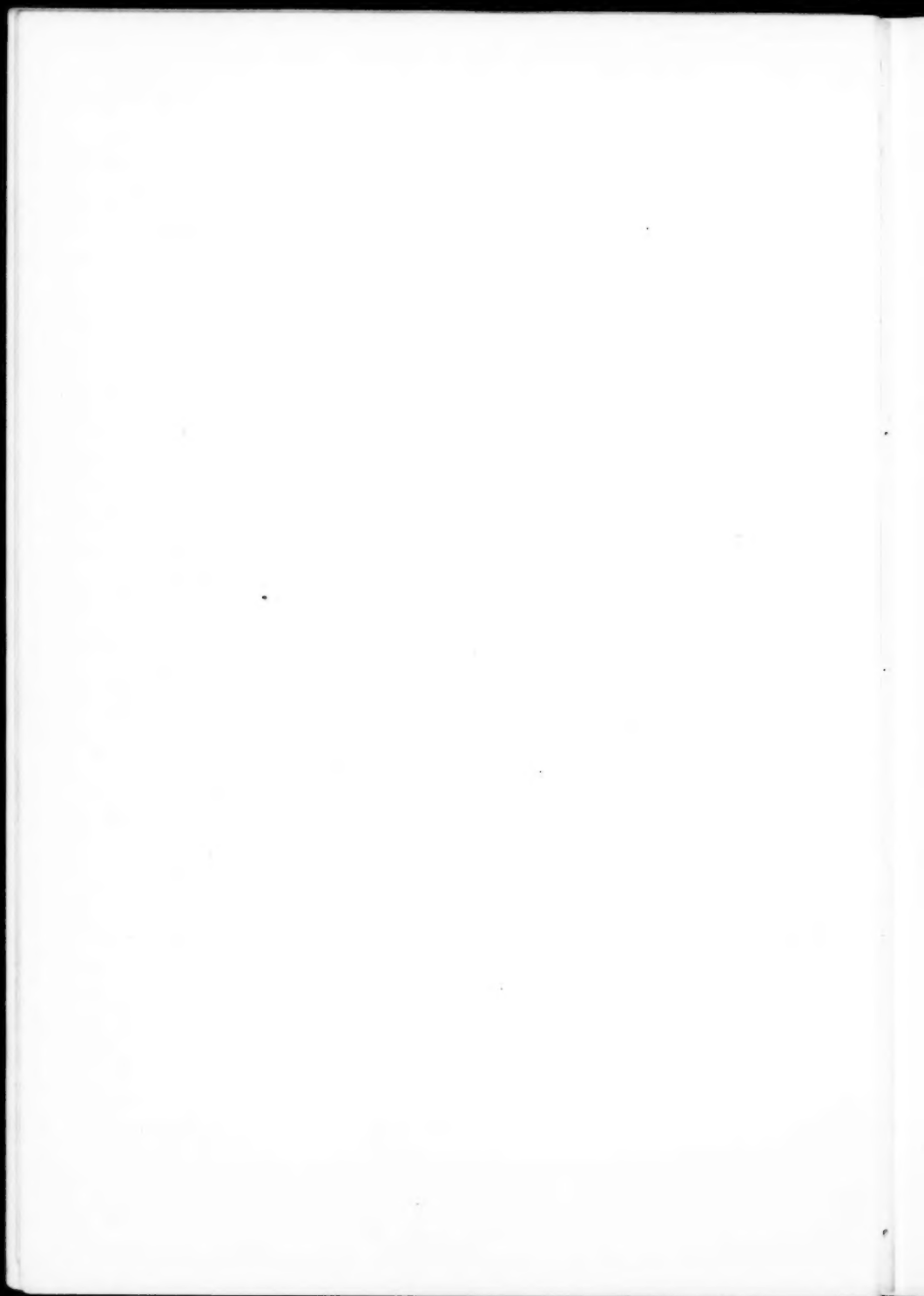
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# ERRATA

Volume III, page 535, line 9: *for* Philipoit, *read* Philippot.  
page 679, line 15: *for* (51), *read* (81).



## PERMEABILITY

BY L. R. BLINKS

*School of Biological Sciences,  
Stanford University, California*

This review summarizes advances in the study of cellular permeability since the previous review of Jacobs (1). The period covered is about three years, from mid-1938 to mid-1941. Important papers, especially from Europe, have necessarily escaped attention and must be included in a later volume. Although the entrance of materials into, or their secretion by, various specialized tissues is noted in some cases, the reader is referred to reviews on these organs (kidney, liver, skin, muscle, intestine, plant roots, storage tissues, etc.) in this and previous volumes, as well as in the *Annual Review of Biochemistry*, for more complete reports on these topics.

The short space available here is fortunately supplemented in the period covered, by the volume on permeability of the *Cold Spring Harbor Symposia* (2); its twenty-eight authoritative chapters discuss such topics as permeability to water, anions and cations, weak electrolytes, radioactive salts, and dyes (and their secretion); electrical measurements of permeability; the chemical and physical composition and structure of the cell surface (especially of the erythrocyte); the permeability of capillaries, skin, and stored blood; salt accumulation by plants; extraneous coats; electrophoresis; the binding of ions by cell surfaces; and models of cell surfaces. In addition there are chapters on related chemical and physical topics, such as free and bound water, chemistry of the lipids and proteins, x-ray studies of lipid-protein systems, and the mathematical treatment of cell permeability.

Other recent reviews include those by Jacobs (3), Stiles (4), and (on the properties of the cell surface) Harvey & Danielli (5). Fenn has included material on permeability in his review on potassium (6), as has Krogh in his book on osmotic regulation (7). A useful summary of data on permeability has been announced (8), although it was not received in time for this review; Kylin (8a) has also tabulated values of algal permeabilities.



*Formulations.*—There is an increasing tendency toward mathematical analysis of permeability, sometimes with the aid of data from distinctly different fields. An example is the calculation of permeability to oxygen, by Rashevsky (2a), using data from respiration measurements (see below). This is but part of his mathematical treatment of diffusion phenomena in two recent books (9, 10). Diffusion mathematics are also discussed by Reiner (11) and Landahl (12). Rashevsky makes a timely contribution in his discussion of the units of measuring or expressing permeability—which he finds (as will the reader of this review) expressed in a multiplicity of terms. Since the diffusion dimensions ( $l^2 \cdot t^{-1}$ ) reduce to  $l \cdot t^{-1}$  when the thickness of the membrane is not known, permeability ( $h$ ) can be simply expressed as cm. per sec., in which units Rashevsky gives his values for oxygen. It would be a great convenience if all workers on permeability would adopt some such simple unit for ready comparison of data.

Other mathematical treatments include those of Manegold (13) on membranes in general; Barrer (14) on activated diffusion; and Danielli (15), who calculates the penetration of substances across a lipid film on the basis of single or multiple energy jumps.

Several other papers (16 to 20) deal specifically with mathematical problems of permeability, and many of the experimental papers include mathematical treatment of the results.

*Methods.*—Unquestionably the greatest revolution in method during the period reviewed has been the application of artificially radioactive elements as tracers of permeability and salt accumulation. Only one reference on this method was included in the previous review (1)—that of the pioneering study of Brooks; the bibliography is now long and growing, as shown in general reviews on these elements (21, 22, 23, 24) as well as by the many papers quoted here [see (2b, c)]. Radioactive potassium, sodium, rubidium, and bromide have been most frequently employed so far, but many others are available, and will inevitably lead to a greater understanding of many problems. This will be especially the case when radioactive carbon can be introduced into organic substances. Two problems however arise: (a) distinguishing "isotope equilibrium" (with the same element already present in the cell) from further accumulation, which may still necessitate chemical analysis; and (b) the possible effects of the isotopes themselves. Some difference in the accumulation of potassium isotopes has already been reported



(25, 26, 27), and the radiation given off by the element either outside or inside the cell may alter permeability. More than one millicurie per liter decreased penetration of sodium in *Nitella* (28) and thirty millicuries almost abolished it. The sensitivity may vary with different cells and different elements. Contamination with other radioactive elements, e.g., sodium in potassium, must also be considered [cf. Dean *et al.* (114)].

*Physical and chemical analysis of the cell surface.*—Aside from their immediate import for penetration itself, permeability studies have often been used to indicate the nature of the cell surface or "plasma membrane" (29). Indeed, the penetration of substances, the effects of anesthetics, and the mechanical properties such as surface tension (5, 30), and "capping" by oil drops (2d, 2e) had supplied our chief evidence as to the nature of that surface. Direct chemical and optical studies had been largely impossible owing to the extreme thinness and fragility of this surface, and the preponderance of other materials inside the cell. This situation is now remedied in the case of the red blood cell by chemical analysis of the envelope or "ghost," which can be obtained in sufficient mass and purity by improved techniques (2f, 31 to 34). While there may be some question as to whether this residue after hemolysis and washing contains all the "plasma membrane," and nothing else, nevertheless the results have great interest for the student of permeability. Dziemian's comparison of chemical analyses with permeabilities showed little correlation between the penetration of either lipid-soluble or -insoluble substances, and the lipid contents of the cells, whether the latter is expressed as lipid per cc. per erythrocyte, per sq.  $\mu$  of cell surface, or percentages of cholesterol or phospholipid (31). This is contrary to the findings of Erickson *et al.* (34) that among the species studied the erythrocytes which are more permeable to lipid-soluble substances contain more lipid. Dziemian concludes that the differences may lie rather in the arrangement of the lipids, and their relations to other constituents, as in a protein-lipid complex. This throws great emphasis on experimental and theoretical determinations of lipoprotein complex structures. Dziemian calculates that if the lipid were spread in a layer on the surface it would be about 30 Å thick—probably bimolecular. That there is some lipid in the actual surface is strongly indicated by enzyme studies (35): lipases altered the permeability of erythrocytes, while proteinases did not. A reasonably fluid,



extensible surface is indicated by experiments on plant cells (36).

The "analytical leptoscope" (2g) now gives direct optical evidence as to the thickness of erythrocyte envelopes: the lipid is about 50 Å thick, while the protein is about 60 Å. (It is thicker in freshly hemolyzed envelopes.) The probable arrangements and orientations of lipids and proteins as determined by optical and x-ray methods have been described (37 to 43); the reader must be referred to the review by Schmitt & Palmer (2h) for a summary. De Booi (44) has also discussed the properties of lipid-protein complexes in relation to cell membranes.

Although this review has not space to deal with artificial membranes, brief mention may be made of at least one which has promise in the study of permeability, namely bimolecular films formed between two aqueous phases (45). These have been made of protein, both native and tanned, and of lipoprotein complexes, and have displayed appreciable resistance and capacity (46). The resistance and capacity of mono- and multimolecular films of barium stearate have also been measured (although not between two aqueous phases) and found to be in the biological range (47).

*Water.*—The apparent paradox of a ready passage of water through a lipid cell surface is partially resolved by new data (2h) on spacings between bimolecular layers of mixed lipids emulsified with varying water contents. These ranged from very narrow spaces (4.2 Å) in dried lipids to about 85 Å in the presence of 75 per cent water—spaces more than ample for the penetration of water-soluble materials and water if some of them happened to exist as "pores" rather than as spaces between laminae parallel to the surface. However, a pore system is not necessary, since a completely liquid phase such as guaiacol transports water readily (2i); it even moves against an apparent concentration gradient in a process called "anaphoresis" (48).

The permeability of living cells to water has been recently reviewed (2j); tables summarizing most of the data, including new determinations, are presented (49). Values (in cu.  $\mu$  of water per sq.  $\mu$  cell surface per min. per atm. difference of osmotic pressure) are as follows: 0.1 to 0.4 for several echinoderm egg cells; 0.4 to 0.7 for annelid and mollusc eggs; 0.12 to 0.25 for a ciliate protozoon; 0.16 to 0.55 for several plant cells; 0.4 to 1.0 for vertebrate fibroblasts; 0.3 to 1.3 for leucocytes; and 2.5 to 3.0 for erythrocytes. A similar value (0.5) was found for an annelid egg, *Chaetop-*



*terus* (50); this increases slightly on fertilization (to 0.6). An increase of water permeability of *Strongylocentrotus* eggs also occurs on fertilization (51).

An ingenious flotation method of determining water loss from the large plant cell *Tolypellopsis*, without actual plasmolysis (52), gave a water permeability value of  $1.08\mu\cdot\text{atm}^{-1}\cdot\text{min}^{-1}$ . (This comes to the same dimensions as those given above and the values lie in their general range.) Bachmann (17), recalculating older work on plant cells, arrived at water permeability values between 0.22 and 119 in a variety of cases, the units here being given in the form sq. cm. per day per mole per cc. The most reliable work, that of de Haan on deplasmolysis of onion cells, gave 0.43 for the entire plasma permeability; many varied between 0.24 and 1.75, figures which are within the range of the diffusion values of various materials in gels or aqueous solutions.

The exit of water has also been observed from the large plant cell *Chaetomorpha* by plasmometric methods, the cell volume also being measured with a dilatometer and the outside solution studied by refractometry (53). These methods were well adapted to follow rates, but unfortunately only equilibrium conditions were reported.

*Valonia* and *Halicystis* cells can be employed as "living osmometers," the increase of volume due to water intake being directly observed in inserted capillaries (54). The velocity constant of water entrance was fairly uniform in concentrations down to about 50 per cent sea water, below which it fell. It had an average value of about  $3.0 \times 10^{-5}$  cm. per min. (or  $0.3\mu$  per min. which is in the range given above for other cases).

A reversed procedure has also been employed (55); instead of allowing water to enter and swell the cells, pressure was applied to plant tissue and fluids squeezed out. Slow application of pressure drove out almost pure water. The applied pressure agreed with the hydrostatic pressure of the tissue, and also with plasmolytic values, but not with the osmotic pressure of the cell sap, which was as little as one tenth the other values. Some continuous diffusion process (endosmosis of water or other mechanism) may serve to maintain the turgor. A direct measurement of turgor has also been developed for *Nitella* cells (56), which may be useful in studying permeability.

Heavy water has been used for following the movement of water from capillaries to tissues (56a); equilibrium was reached



within one-half minute with the extracellular spaces, and within one-half hour with the entire body—presumably the cellular water.

*Gases.*—Gases such as oxygen and carbon dioxide are, because of their very rapidity of entrance, difficult to study by quantitative methods. High permeabilities have long been inferred from the speed of luminescence, oxidation of reduced dyes, hemoglobin, cytochrome, etc., when oxygen is admitted to anaerobic cultures. A direct method now available for oxygen exit in photosynthesis (57) permits rapid recording. It shows but slight lag between illumination and arrival of oxygen at the electrode just outside the cell wall; a high permeability to oxygen is indicated.

An indirect calculation using steady state values of respiration under different oxygen tensions (2a, 10) yields permeabilities for oxygen as follows: *Arbacia* eggs,  $5.2\mu$  per sec.; *Chlorella*,  $1.1\mu$  per sec.; and luminous bacteria,  $550\mu$  per sec. The reason for the high value of the latter is not clear; some of the assumptions used in the calculation may be wrong.

Although concerned with partly nonliving walls and cutinized elements, values for seed coats (*Cucurbita pepo*) have also been obtained (58). They range from 0.35 (oxygen), and 0.31 (nitrogen) to 3.0 (carbon dioxide) in the outer membrane; and 4.3 (oxygen), 3.2 (nitrogen), to 15.5 (carbon dioxide) in the inner membrane. (Values are in cc. per sq. cm. per hr. per atm. pressure difference.) The curious "gas vacuoles" of the blue-green algae should be interesting objects for gas permeability studies (58a).

*Nonelectrolytes.*—The penetration of these substances on the whole follows simple diffusion laws, concentrations tending to reach equality, without accumulation. The following values are summarized (49) in  $10^{-15}$  moles per sq.  $\mu$  per min. per mole per liter concentration difference: for ethylene glycol, 14.3 in *Chaetopterus*, 15.6 in *Cumingia*, and 3.5 in *Arbacia*. For glycerol the value in *Chaetopterus* is 6.2, almost half as fast as for ethylene glycol, while in *Arbacia* it is only 0.03, the latter value being more in agreement with most observations on this slowly penetrating substance. A method using isotonic solutions (59) gives the penetration of ethylene glycol into *Arbacia* eggs as  $2 \times 10^{-15}$ .

An optical method (60) used with ox erythrocytes showed at  $20^{\circ}\text{C}$ . a permeability of  $0.017 \times 10^{-15}$  for glycerol, which is well known to penetrate more slowly than ethylene glycol. The permeability of red cells for monosaccharides showed specific differ-



ences: human erythrocytes allowed fructose and sorbose to penetrate most slowly, while these same sugars penetrated dog erythrocytes especially well. Pentoses penetrated more rapidly than hexoses. Sugar permeability is so slight in rabbit, rat, and dog erythrocytes that it does not equal glycolysis; therefore the ratio of plasma sugar to blood sugar does not give a key to the permeability in most cases. A discrepancy in the distribution of glucose between cells and serum may involve permeability (61).

A parasitic protozoon (*Gregarina*) has been studied (62) with plasmolytic methods. It showed very slight permeability to salts, amino acids, and mannitol. But other nonelectrolytes penetrated at the following rates: glucose, 0.03 to 0.15; glycerol, 0.9 to 1.2; ethylene glycol, 2.0 to 6.1; urea, 1.36 to 3.5; and propylene glycol, 6.8 to 8.97 (all in moles  $\times 10^{-15}$  per sq.  $\mu$  per min. per mole per liter). Water was in the range reported above (0.06 to  $0.58\mu$  per min. per atm.). On the whole, this cell was more permeable to substances of high lipid solubility than to those of low, even though the former may have larger molecules. In this it resembles most of the other cells listed, but it is more permeable than most others to substances of low lipid solubility and large size such as glucose and fructose.

Specific differences in animal cells recall the "permeability series" and "glycerol vs. urea types" of plants, discussed in the previous review (1). These have been further studied (63, 64, 65) with the purpose of clarifying the physicochemical reasons for the differences. The quotient  $Q$  (ratio of permeability to urea to permeability to glycerol) varies between 6.0 and 0.4, and changes in a complicated fashion with acidity (66). A splitting of urea to ammonia and carbon dioxide by urease was a conceivable source of acidity change, but was not found significant. Other causes such as aging, frost-hardening, etc., might result in pH changes, which cause "swelling" of the membrane. These are aided by urea but antagonized by glycerol, with consequent changes in  $Q$ . Thus urea can increase the permeability to glycerol in *Gentiana*, but decrease it in *Polygonum*, depending on the part of the pH curve concerned. Calcium chloride and dextrose decreased the permeability of plant cells to glycerol and urea, while potassium chloride increased it (66a).

Acid also affects the permeability of erythrocytes (67): lowering the pH from 7.4 to 5.4 greatly decreases the rate of entrance of



glycerol, while raising it again restores normal permeability. The same pH effect is obtained to a less extent with ethylene glycol, but not with many other substances.

Injurious effects of thiourea, often used as a penetrating non-electrolyte, have been found in *Gentiana* (68). Contrary to earlier reports, permeability differences have not been found in *Hippuris* water and air cells (69).

*Weak electrolytes.*—These have long been known to penetrate cells more readily in the undissociated form than as ions. The increased effects of nicotine at higher pH values (70, 71) illustrate this anew. Fluoride penetrates yeast cells most rapidly at low pH, the undissociated acid molecule entering, and leaving a higher pH in the solution outside (72). Pyruvic acid also appears to penetrate yeast better at low pH (73). The free penetration of erythrocytes by cyanide (74) is presumably as the undissociated gas molecule at physiological pH values.

Jacques (75) derived a "permeability constant" for the entrance of ammonia into *Valonia*; this had the value 0.0067 in the dark, but dropped to 0.0026 in light, probably because of a lower concentration of an unspecified acid in the membrane with which ammonia could combine. Despite this, entrance of ammonia was faster in light, because photosynthesis raised the pH of the sea water. The exit is more complicated and may involve urea or amino acids.

Penetration of molecules (of carbon dioxide or ammonia) can "catalyze" the entrance of ordinarily nonpenetrating ions by supplying exchangeable ions after entering the cell (76). This may have wide implications in accumulation (2k).

*Dyes.*—These have long been used as convenient weak electrolytes for permeability studies. Those which do not penetrate are as instructive as those which do. Sulfonated acid dyes generally penetrate poorly: orange G and cyanol did not enter living cells of *Tolypellopsis* or *Aspergillus* (contrary to Bünning's report on the latter) during exposures of a week (77). Phenol red does not enter living cells of muscles (78) but is restricted to intercellular ("chloride") spaces; it only appears in injured or killed cells (in the latter mostly in cells made acid). Cordier (79) has studied the penetration of acid dyes in young trout.

Basic dyes have long been used as vital stains, and penetrate better at high pH values. Drawert has reported general agreement



with this principle (80): living plant cells poor in free fatty acids absorb the dyes only as neutral molecules of the dye base; in this they resemble organic "hydrophobic" solvents (chloroform, toluol, etc.). Cells richer in free fatty acids (or tannin) also took up molecules of the dye salt (like solvents containing oleic acid). Drawert therefore emphasized the partition coefficient of the dye between cell interior and exterior, as well as permeability, in determining the staining. Indeed, he ascribes the poor penetration of sulfonated dyes to low partition. He was concerned with equilibrium conditions, but partition coefficients within the membrane can determine rates of penetration as well.

The uptake of over seventy dyes by *Elodea* (81) is conditioned by their acidic or basic nature (bases penetrating better); by their degree of dispersion, molecular size, colloidalilty; and most strongly by lipid solubility. The penetration of thirteen acid dyes (82) into ciliated epithelial cells was conditioned by size: only penetration of dyes smaller than 6.4 Å in radius occurred. In muscle cells and bladder membrane the upper limit was 7.3 Å (the size of eosin lying about here). Lipoid solubility did not control entrance here.

In addition to pH, various salts and other conditions determine the penetration of dyes (83 to 88), sometimes through an effect on the dyes, sometimes on the cell surface. The opposite effect, alteration by dyes of permeability to other substances, also occurs (89): *Elodea* cells lightly stained with neutral red have an increased urea permeability, but when deeply stained, show a decreased permeability to urea. Permeability to glycerol was decreased by both; methylene blue decreased or even abolished penetration of urea and glycerol. Eight other plants, however, did not show this effect. One dye can also suppress the secretion of another in frog liver (21); this review summarizes a series of important findings on the influence of structure and position of polar groups in dyes upon their secretion by liver and kidney (90, 91, 92). Their applications to cellular permeability should be most valuable.

Neutral red and phenol red have continued to be employed in study of kidney function (93, 94, 95), the former moving by a diffusion process independent of metabolism, the latter being "actively" secreted. Fluorescent dyes have come into greater use (96, 97, 98, 99), being detectable in very low concentration under ultraviolet radiation. Acid dyes like fluorescein penetrate only at



low pH and hence are useful for tracing extracellular movements in vessels, walls, etc. (97). Berberin, and a new dye, acridine orange, are basic and enter more readily, giving good differentiation of structures (membranes, etc.). These should be valuable tools, although the possibility of photodynamic action must be considered (see below). Localization of other dyes in various parts of cells (granules, nuclei, etc.) has also been described (100, 101, 102, 103). An increase in permeability to dyes has been confirmed in sea urchin eggs after fertilization (51, 104).

A useful summary of the vital staining of plant cells has been given by Küster (105).

*Strong electrolytes.*—Erythrocytes have long been known to have an exceptionally high permeability to anions, permitting a ready exchange of chloride for bicarbonate, etc. The penetration of sulfate in exchange for chloride (2*m*) is half completed in 9 sec. (rat), 18 sec. (rabbit), or 25 sec. (beef) at pH 7. Lowering the pH had a marked effect, at pH 5 the exchange being as much as one hundred times slower than at pH 8. This is possibly ascribable to a closer packing of the lipoid film under acid conditions. On the other hand at pH 8 the membrane becomes so porous that even cations leak through; no evidence for a pH reversal from anion to cation selective permeability was found (as once claimed by Mond). Many data about the normal and abnormal permeability of erythrocytes to cations have recently been obtained, and are summarized by Davson (2*n*). Altered cation permeability can be due to dilution of the medium, alteration of its potassium content, sugar, or various lyotropic salts (106, 107); since one or another of these changes almost always has to be made in altering gradients, the difficulties of maintaining the cells in a normal condition are obviously great. In addition the permeabilities to sodium and potassium may change in different degree or even in different directions (106).

The advent of radioactive tracers has aided this study, in that a minimum of change (that of one isotope for another, in normal concentration) has to be made, Brook's first report (108) showed some penetration of radioactive potassium into rabbit erythrocytes, but little of sodium. Later work (109, 110) indicated low permeability to potassium, for although after one day the corpuscles contained about 60 per cent as much radioactive potassium as the



same weight of plasma, this is about one thirtieth of what was to be expected on the basis of its partition between the potassium contents of cells and plasma. At this rate the bulk of the potassium in the corpuscles of a rabbit would not be replaced in the lifetime of those corpuscles. Slight exchange of sodium and potassium was also reported in man (111), but dog corpuscles were found quite permeable to radioactive sodium (112).

More recent work (113, 114) points to a definite exchange of radioactive for normal potassium across the surfaces of erythrocytes in man, rabbit, and rat. "Diffusion coefficients" of  $0.2$  to  $1.0 \times 10^{-3} \text{ min.}^{-1}$  were obtained; i.e., isotope equilibrium reached  $1/1000$  to  $1/5000$  completion per minute. While detectable, this is still low permeability—only one millionth as great as the permeability to anions. In human erythrocytes in ten hours some 15 per cent of the potassium had exchanged *in vitro*. [Eisenmann *et al.* (111) found 4.4 per cent exchange in four hours.] The exchange appears to be more rapid *in vivo* than *in vitro*. Other workers (115 to 119) also agree in finding a permeability to potassium, though a much smaller one to sodium. Dean *et al.* (114) suggest that impermeability to sodium prevents the potassium from leaking out by exchange. It is also possible that a slight metabolism (20) enables the erythrocyte to go on accumulating potassium at just the rate at which it leaks out—a carry-over from active accumulation in the bone marrow.

Dean *et al.* (114) suggest that the low apparent permeability of erythrocytes to potassium, reported by Hahn *et al.* (110), might be due to high concentrations of radioactive sodium in the sample.

In frog muscle a slow exchange of potassium occurs (110): after twenty-four hours about one twentieth of the potassium within the cells had exchanged with the radioactive isotope outside. Radioactive sodium enters the muscle cells of rats deprived of potassium (120); and frog muscle loses potassium in potassium-free Ringer's solution, regaining it from normal Ringer's (121, 122).

The axoplasm of squid nerve gains chloride after its dissection from the animal and immersion in sea water (123). This is interpreted as a readjustment of steady state in the new environment, not as a change of permeability due to manipulation. Donnan equilibrium forces may be involved in the chloride exchange, since high concentrations of organic anions (probably indiffusible) have



recently been established in this cell (124, 125, 126); they may also be operative in the bioelectric potential [as they appear to be in *Halicystis* (127)].

Salt permeability has also been investigated with radioactive tracers in frog skin (128), placenta (129), capillary walls (130), muscle (131), and marine eggs (132).

In plants the penetration of radioactive elements has been studied almost entirely in *Nitella* cells (2b, 20, 28, 108, 133, 134, 135, 136); and in the roots of higher plants (2c, 137 to 141). *Nitella* shows a rapid intake of potassium, which may reach concentrations several times that of the environment within a few minutes. This is localized almost entirely in the protoplasmic layer, penetration into the vacuole being much slower—a good instance of high permeability and low “intrability.” Although the protoplasm was not analyzed for total potassium, the height of the first cusp suggests there may be three or four times as much potassium within the protoplasm as outside. However, this is but temporary and within fifteen or twenty minutes much of it is lost. A curious cyclic “gain” and “loss” of potassium then ensues for several hours before a permanent rise occurs.

The loss of radioactive sodium from *Nitella* (135) is very slow in distilled water, but more rapid in salts, the order being lithium > sodium > potassium > cesium; the reverse order is found for the loss of potassium however. The speed of all these movements points to a higher permeability to salts than had formerly been assumed for *Nitella*: from  $10^{-4}$  to  $10^{-7}$  mole per sq. cm. per sec., which is in the range of water and small nonelectrolytes. The experiments do not indicate whether the salts penetrate as molecules or ions, although an ionic exchange is assumed by Brooks. Earlier figures were based upon penetration across the entire protoplasm; it now appears that the low permeability is located at the vacuolar membrane or tonoplast. The problem therefore still remains as to the penetration and accumulation of salts in the sap—perhaps to an even higher concentration than in the protoplasm.

Collander (142) has contributed a long and careful study on such salt accumulation in the vacuoles of closely related plants (*Chara* and *Tolypellopsis*). Entrance of cations occurred in the order potassium > rubidium, lithium > cesium > strontium > manganese. Sodium, magnesium, and calcium were not absorbed appreciably. The movement of sodium was about 3,000,000 times



slower, and the rubidium-potassium exchange 1,000,000 times slower, than in free aqueous diffusion. There is evidently still a large hindrance to diffusion of salts, which is doubtless at the vacuolar membrane. Light and oxygenation favored absorption, but pH had little influence on absorption of lithium. Bromide was absorbed faster than lithium, sulfate slower. In contrast to this, an analysis of *Hydrodictyon* sap shows high sulfate content (143).

Other studies on the salt permeability may be only mentioned: marine algae exposed to tidal change are very permeable to salts (144) as are also diatoms (145, 146). The halophyte *Suaeda maritima* on the other hand is very impermeable and resistant to salts (147). A rapid adjustment of volume in dilute or concentrated sea water indicates that *Amoeba mira* is permeable to salts (148).

*Relations to metabolism.*—In several cases above the intake of water, dyes, salts, etc., appeared to be connected with respiratory or other metabolic activity. The energy for accumulations above the environment can hardly come from any other source. A metabolic role in the maintenance of potassium in the erythrocyte is suggested by the uptake of this element at 37° in blood cells which had lost it during storage at 2° to 5° (149). This recovery is not as marked at 25°. No recovery of potassium occurred in the presence of 0.02 *M* sodium fluoride, which indeed caused a loss of potassium even at 37°. In other experiments (150) potassium re-entered at 37° for some five hours, after which it escaped again. This loss coincided with the completion of glycolysis, and could be delayed by adding glucose, or hastened by adding fluoride.

Wilbrandt (151) investigated the connection with glycolysis, likewise finding that poisoning with fluoride or iodoacetate rendered erythrocytes permeable to cations. But he concludes that this is because metabolites then accumulate which poison the cell, and duplicated the effects by adding various normal and abnormal glycolytic products. Much the same conclusion was more recently reached by Davson (152). Wilbrandt (60), on the other hand, found that the selective permeability for sugars was not altered by iodoacetate or fluoride.

Potassium gain and loss in muscle, on the other hand, appears to be rather independent of metabolism (153 to 155), potassium entering against a concentration gradient just as well anaerobically as aerobically. Muscles also retain their potassium in nitrogen, at least until injury or death sets in; there is no evidence that



it is maintained there by the continuous expenditure of energy. Neither did inhibition of glycolysis accelerate the loss of potassium (until the onset of rigor).

A close connection between salt intake and carbohydrate metabolism is reported in yeast (156), potassium entering during glycogen formation and leaving with breakdown of glycogen (cf. also 19). This may be connected with phosphoric esters of the sugars; it is not ascribed to permeability changes due to end products of metabolism. Cyanide and fluoride had little effect, but iodoacetate was very inhibitory.

Both roots (137 to 141) and potato tubers (157) accumulate potassium and other elements only aerobically, retaining or losing it slowly under anaerobic conditions. Connections with protein, amino acid, organic acid, and other metabolic syntheses have been suggested. These may be the radicals to which potassium must first be attached in the protoplasm, and are therefore concerned with gradients or driving forces, rather than with permeability proper. It is not easy to separate the two factors, but evidence for altered permeability as such under anaerobic conditions is accumulating.

The behavior of yeast, briefly noted before (1), has now been reported at length (72, 158, 159). Fluoride penetrates more readily under anaerobic than aerobic conditions, as shown both by direct chemical tests (72) and by its effects on respiration and fermentation. Permeability can also be increased by exhaustion of the substrate or by treatment with thioglycollic acid, and decreased again by restoring glucose. Various oxidation-reduction systems, however, failed to produce any permeability change [this agrees with the absence of their effects on the bioelectric properties of *Nitella* (160)]; probably some anaerobic metabolite is responsible, as suggested by Wilbrandt (151) for erythrocytes. The relations of permeability of yeast to pyruvic acid under various metabolic conditions have also been discussed by R nnstrom *et al.* (158, 159). Smythe (73) found that pyruvic acid was utilized aerobically at pH 7.0, but anaerobically only at pH 4 or less. Possibly the permeability to pyruvate ions was decreased by low oxygen tension and the acid could then penetrate only as the undissociated molecule. Increased permeability to sugars (especially glucose) occurs in potatoes under anaerobic conditions, particularly after several days, the loss of stored sugars being increased as much as ten-fold (161).



The entrance and accumulation of asparagine in plant cells (162) occurs in aerobic, but not in anaerobic conditions; whether the latter is due to decreased permeability to asparagine, or to failure of an accumulatory process is not yet clear. The penetration of glycerol was not altered.

Roots permit less passage of water under anaerobic conditions, this fact indicating a decreased permeability (163), although active transfer may be involved. Alterations in water passage may also be "induced" in the root from the tops or cut surfaces (164). A lowered permeability to salts under anaerobic conditions is indicated by electrical measurements in *Halicystis* (165); since weak acids produce the same effect, an internal increase of acidity by fermentation may be responsible for the anaerobic effect (2*p*). But *Valonia* is much less influenced by low oxygen tension, and *Nitella* scarcely at all (166). Thus there appear to be very large differences in metabolic influences. Earlier work has shown that anaerobiosis has little effect on the permeability of erythrocytes, and conversely, swelling of the cell with increase of surface does not change respiration or glycolysis (167). The chemistry of fermentation as well as of the cell surface may determine the extent of these interrelations.

*Poisons and drugs.*—Ethyl urethane, and copper and mercury salts greatly reduce the permeability of human erythrocytes to glycerol (67); the effect is reversible, especially by addition of a trace of serum or hemolyzed cells, presumably to precipitate the heavy metals. Tannin also reduces their permeability to ammonium salts (though not very reversibly). Short exposures to saponin render chicken erythrocytes more permeable to lipoid-soluble as well as -insoluble substances (168); the penetration of large molecules (malonamide) was increased more than that of small (glycerol). Saponin permits more ready penetration of strychnine through frog skin (169), and seems to facilitate its own entrance into branchial epithelium (170), its entrance going up faster with concentration than the diffusion laws predict.

Alcohols (methyl through amyl) alter both the conductivity of frog skin and its permeability to thiocyanate (171). Low concentrations produce a reversible increase, intermediate concentrations a reversible decrease, and higher concentrations an irreversible increase of permeability. Hexamethylenetetramine has been compared in toxicity and penetrability on various plant cells (172), but no close parallel was found. Veratrine increases the permeabil-



ity of frog skin to sodium chloride (173); leucotaxine increased the permeability of *Arbacia* eggs to water by about 50 per cent (174). On the other hand (175) various carcinogenic and related compounds were found to have no effect upon the permeability of marine eggs or erythrocytes, either to water, or to eight different solutes (nonelectrolytes, and weak and strong electrolytes). Sulfathiazole has been found in lower concentrations in human erythrocytes than is sulfapyridine under identical conditions (176), but this may be a difference in equilibrium state rather than of permeability.

*Physical agents.*—Mechanical changes such as stretching or contracting the surface can alter permeability. Thus, although unfertilized *Arbacia* eggs can be almost flattened without rupture, slight pressure on fertilized eggs may cause release of calcium from the cortex (177). Permeability changes produced by shaking (178) are ascribed to thixotropic effects on the surface. Centrifuged cells plasmolyze at the plastid-rich end (179).

Temperature effects may be large without indicating chemical processes: thus the penetration of nonelectrolytes into *Tolypellopsis* (180) follows ordinary diffusion laws, yet  $Q_{10}$  values ranged from 2.55 for urea to 8.9 for hexamethylenetetramine.  $Q_{10}$  values paralleled molecular size rather than lipoid solubility. A  $Q_{10}$  of 2.4 occurred in the penetration of radioactive potassium into erythrocytes (114), and an Arrhenius constant  $\mu$  of 23,000 calories in the exchange of chloride for sulfate in erythrocytes (2m, p. 26). Permeability changes to potassium, due to temperature, have also been suggested for the bioelectric effects of warming or cooling in *Valonia* (181). The permeability of carrots to water (182) on the other hand has a very low  $Q_{10}$  (1.1). More drastic changes may of course be induced by temperatures out of the normal physiological range; some of these have been described (2q) for frost-hardened plants. Potatoes also lose their semipermeable properties after twenty-seven hours at 48°, or rapidly at 60° (183). Related to frost hardening are drought resistance (185), wilting (186), and dehydration by sucrose (187), all of which alter the texture or permeability of the plant cell.

Light as such has little effect on the permeability of *Hippuris* to glycerol (69), or on *Sedum* (188), although urea penetrated three times as fast in green illuminated leaves as in darkened, etiolated ones. There is a small (8 per cent) but apparently con-



sistent increase of water entrance into cells of carrot when brightly lighted (182); this is ascribed to increased endosmotic flow resulting from altered bioelectric potential (189); carotene may be implicated, as in many light sensitivities. Light shortens plasmolysis time in onion cells (190); it also increases the absorption of salts (hence of water) in impaled *Halicystis* (54). Its bioelectric effects in *Valonia* and *Halicystis* (127, 181) have been ascribed to photosynthetic alterations of oxygen and of pH, which in turn alter ionic mobilities in the cell surface.

Certain dyes induce photodynamic alterations of permeability (191, 192, 193), probably by oxidation of the membrane; it can be inhibited by sulfite or serum. This is doubtless the origin of photodynamic alterations of bioelectric potential (194). The membrane effects may even become visible in amoebae (195). Ultraviolet alters permeability, especially of outer surfaces, leading to tonoplast plasmolysis (196) or loss of calcium (197). X-rays increase the penetration rate of sodium and potassium in erythrocytes to  $2.2$  and  $2.8 \times 10^{-17}$  moles per hr. per sq.  $\mu$  per mole per liter (198). The permeability to sucrose and magnesium was not increased, and that to other substances only slightly: water, 20 per cent; thiourea, 6 per cent; and ethylene glycol, 3.5 per cent. The effects are ascribed to increased affinity of the membrane for water.  $\gamma$ -rays from radium (199) as well as from radioactive sodium (28) reduce the permeability of plant cells to several solutes.

The effects of electric currents must be left to reviews of bioelectric phenomena; if large enough there is little doubt that they can increase permeability (200), and a rapid diminution of resistance on stimulation is now well substantiated in *Nitella* (201, 202, 203, 204), as well as in nerve (205). Rectifications can be due to ions of different mobilities on opposite sides of membranes (206) or to alterations at the cathode, but it is doubtful whether a potential as such, without current flow, can alter permeability (cf. 106, 207).



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SCHOOL OF BIOLOGICAL SCIENCES  
STANFORD UNIVERSITY, CALIFORNIA



## THE PHYSIOLOGICAL EFFECTS OF NEUTRON RAYS

BY PAUL C. AEBERSOLD AND JOHN H. LAWRENCE

*William H. Crocker Radiation Laboratory, University of California,  
Berkeley, California*

With the demonstration of the existence of neutron rays in 1932 (1) a new type of radiation appeared which, because it possessed the unprecedented combination of great penetration and the ability to produce ionization in extremely dense loci, offered new opportunities for the study of problems in radiation biology. Although it was realized by many that these newly discovered rays could produce biological effects and that there were unique possibilities for their use (2), it was several years before sources were developed sufficiently strong to demonstrate their biological action.

A neutron is a small particle of matter as heavy as the nucleus of a hydrogen atom but not having any electrical charge. It does not occur free in nature but only as one of the fundamental building blocks in all of those atomic nuclei which are heavier than ordinary hydrogen. When certain types of disintegrations of atomic nuclei are brought about, neutrons are ejected with high energy. These energetic neutrons are called fast neutrons, or for radiological purposes, neutron rays. Because they are uncharged they do not ionize directly, which fact accounts for their ability to penetrate into large depths of matter. The ionization they cause results from their chance collisions with the nuclei of atoms. The recoiling nuclei, being massive and charged, ionize heavily. In tissue, neutrons produce mainly recoil hydrogen nuclei, or protons, which cause ionization about a hundred times more dense along their paths than do the electrons which result from x-irradiation. This different character of the ionization produced in tissue by neutrons accounts for the interest in the biological effects of neutrons.

The first sources of neutrons were made by mixing radium or radon with beryllium. Here, the naturally available alpha particles are used as the bombarding atomic bullets with which the beryllium nuclei can be disrupted and fast neutrons emitted. With a source using as much as a gram of radium the neutron intensity is



so small that very long irradiation periods would be required to demonstrate biological effects. However, the most serious obstacle to the use of such sources for biological experiments is that the ionization produced by the gamma rays from the radon or radium is around a thousand times greater than that produced by the neutrons. Thus these naturally available sources were not suitable for biological investigations.

Nuclear bombarding apparatus was available in 1932 which could produce energetic hydrogen nuclei (protons) and helium nuclei (alpha particles) but with these particles and the energies then obtainable, the neutron yields were not large. It was not until the discovery of deuterium and the consequent use of the deuterium nucleus, the deuteron, as a high energy bombarding particle that it was found that extremely high yields of neutrons could be obtained especially when beryllium was bombarded. It was noted that the yield of neutrons rose rapidly with the energy of the bombarding deuterons. Fortunately, higher bombarding energies were constantly being reached by the development of the cyclotron by E. O. Lawrence and his associates (3). By the summer of 1935, the 27-inch cyclotron was accelerating deuterons to an energy of 3.5 million volts and the deuteron current of five microamperes hitting a beryllium target produced a source of neutrons hundreds of times stronger than any previously attained.

As nothing was known of the physiological effects of neutrons and of the magnitude of dosage to cause injury there was danger (with such a strong source) of overexposing the personnel of the laboratory. Accordingly an investigation into this problem was started in the summer of 1935 (4). Because of the well-known blood count changes following radiation exposure, blood studies were used and albino rats were chosen as suitable experimental animals. The rats had to be exposed fairly close to the beryllium target source of neutrons and the exposure measurements were arbitrary and not highly accurate. However, when exposures were measured in the same manner as protection measurements are made in the case of x-rays, only one twentieth as much exposure with neutrons as with x-rays was needed to produce comparable changes in the blood counts or lethal effects on the animals. It was realized that this measurement of neutrons, largely by their ionization of air, was not comparable to tissue ionization in the same relation as it is for x-rays. However, inasmuch as factors



estimated to correct for the relation between tissue ionization and the exposure measurements were not large enough to explain entirely the greater sensitivity to neutron rays, it was concluded that the neutrons are more efficient per unit of ionization in the tissue. A quantitative difference was thus the first difference noted between the biological action of x-rays and neutron rays. The qualitative effects, on the irradiated animals and their blood were grossly the same.

Simultaneously, in the studies of R. E. Zirkle, who became interested in neutron biology because of his biological experiments with alpha particles (5), wheat seedlings were irradiated with the same neutron set-up as discussed above (6). It was found, surprisingly, that the growing roots of the wheat seedlings were retarded a given amount in growth by only one fortieth as much exposure with neutrons as with x-rays. In other words, the seedlings were twice as sensitive to neutrons when compared to x-rays as were the rats. These results indicated that the comparative effects of neutrons and x-rays are quantitatively different for different biological tissues. The next step was to use different biological objects and compare the sensitivity of the various objects with respect to one another both with x-rays and neutron rays. Not only is this point of interest in experimental radiation biology, but it has important clinical implications. Should neutron rays prove to affect certain tissues (e.g., neoplastic) more than other tissues (e.g., normal) than is the case for x-rays, they might have advantages in therapy.

Inasmuch as there was considerable difference in size of the objects (rats and seedlings) in the first work, the investigation of the comparative sensitivities was continued with small objects so that the small target distance the neutron intensities throughout the organisms would be closely similar. Before summarizing these investigations, it seems wise first to discuss in more detail the properties and measurement of neutrons.

#### PHYSICAL PROPERTIES OF NEUTRON RAYS

*Processes of energy loss.*—The behavior of neutron rays is readily accounted for by considering the two characteristic properties of the neutron, i.e., absence of electrical charge and possession of a mass as heavy as the nucleus of hydrogen (proton). Because of the lack of charge a neutron does not ionize directly. It may



thus penetrate large distances in matter without loss of energy. Only when it hits something massive, such as the nucleus of an atom is it deflected or scattered. The consequence of such a collision is that the neutron transfers some of its energy to the "struck" nucleus. This recoiling nucleus does have a charge and accordingly pulls electrons away from, that is, ionizes, atoms along its path. Thus the ionization produced by neutrons results from secondary ionizing particles—recoil nuclei.

Most of the collisions of fast neutrons with the light atomic nuclei contained in tissue can be considered as collisions between tiny elastic spheres. A proton, because it is about equal in mass to the neutron, can acquire more energy in recoiling from a neutron than can heavier nuclei. For example, in a head-on collision a proton will receive the full kinetic energy of the neutron, which with neutron sources in use may be as high as twenty million electron volts. However, in the average elastic collision only one half of the maximum, or head-on value, is acquired. Heavier nuclei recoiling from elastic collisions by neutrons acquire the following fractions of the kinetic energy which would be acquired by a proton hit at the same angle: carbon 28 per cent, nitrogen 25 per cent, oxygen 22 per cent, calcium 1 per cent, and lead 0.05 per cent. From the relative energy loss to lead and hydrogen nuclei it can be seen that a fast neutron may bounce through large thicknesses of lead without losing much energy, while it will rapidly lose energy in successive collisions in a material rich in hydrogen, such as water or paraffin. This unprecedented difference in absorption by lead and by water was one of the phenomena that led to the discovery of neutrons.

The rapid loss of energy by neutrons in hydrogenous material results in neutrons of very low energies, called "slow" neutrons, which have special properties. The "slow" neutrons are neutrons that have lost energy until they are bumped about only by the thermal motion of the atoms. The energy of the slowest neutrons, or "thermal" neutrons, is only 0.1 to 0.01 electron volts. "Fast" neutrons are generally considered to be those having energies above 100 kev. (kilo electron volts) leaving the range between this energy and thermal energies for "intermediate" neutrons. "Very fast" neutrons with energies above 15 mev. (million electron volts) are also generated with high energy apparatus such as the cyclotron.



One of the special properties of neutrons is the ease with which they penetrate into the nuclei of atoms. The strong electrostatic force that repels a charged particle when it attempts to enter a nucleus does not affect the chargeless neutrons. In fact, the eventual fate of every neutron, since none exists free in nature, is to take refuge in some nucleus.

When the neutron which enters a nucleus is fast, it may lose much of its energy in stirring up the neutrons and protons that make up the nucleus. The same neutron (or another one) may be sufficiently agitated to come out again, but the "struck" nucleus is left "excited," that is, with an excess internal energy. The nucleus returns to normal by emitting the excess energy as gamma radiation. In this case the combined kinetic energy of the scattered neutron and the recoil nucleus is less than that for an elastic encounter by the amount of energy radiated as gamma radiation. This process is called inelastic scatter. For the same angle of scatter the nucleus gets less energy of recoil in this process than in an elastic collision. In biological material, however, the effect of inelastic collisions can be neglected because for hydrogen they do not occur, and for carbon and oxygen elastic collisions predominate. Inelastic collisions are an important source of energy loss only in heavy elements.

In some cases when the neutron enters a nucleus, the newly compounded nucleus is so excited (unstable) that it almost immediately flies apart (disintegrates) and expends the excess energy. Disintegrations by neutrons are known to occur for lithium, boron, and nitrogen. In the cases of lithium and boron one of the particles is an alpha particle and the other is the remainder of the nucleus. In the case of nitrogen a proton is emitted leaving a residual carbon nucleus. The energy released by such disintegrations is sufficient to give the particles several million electron volts of energy. If there were a sufficient concentration of any one of these nuclei in tissue, especially if localized in certain cells, the resulting disintegrations could be an important factor in producing biological damage with neutrons. However, the concentrations are ordinarily so small that the effect of such disintegrations can be neglected. For nitrogen, which is present in tissue in appreciable quantities, it can be calculated that with fast neutron irradiation the disintegrations could account for only 0.5 per cent of the total ionization. Since the emitted particles



in this case are protons and protons already account for most of the ionization by fast neutrons, any special influence of nitrogen disintegrations can be considered negligible.

When a neutron enters into most nuclei, it is captured without the immediate occurrence of a disintegration. In this process, called neutron capture, some of the excess energy of the compound nucleus is given off immediately as a gamma ray. The nucleus then remains an isotope of the original nucleus (one neutron heavier) but is generally still unstable. Since at some time later it returns to normal by emitting matter or radiation, the isotope is said to be radioactive. Radioactive isotopes are formed by neutron capture which emit beta rays, gamma rays, or both with a wide range of half-lives of activity.

Neutrons of low energy are captured to a much greater extent than those of high energy. The reason for this is that a slow neutron spends a much longer time in transit through a nucleus than does a fast one and is thus more likely to be caught. Some nuclei have an enormous capacity for capturing slow neutrons. This capacity is measured by the capture "cross section" which is the effective area presented by the nucleus for capture of an oncoming neutron. Cadmium nuclei have such a large cross-section for capture of thermal neutrons that thin sheets of cadmium effectively stop all thermal neutrons from passing through them, and they can be used as shields against slow neutrons. The process of disintegration discussed above can be considered as a capture of the neutron followed by immediate disintegration. Consequently, it also happens to a much greater extent for slow neutrons. In fact, the boron nucleus has an extremely large cross section for disintegration with slow neutrons.

As will be discussed later, it would be possible by introducing boron into certain tissues to effect irradiation of these tissues by the heavily ionizing disintegration particles resulting from capture of slow neutrons with little irradiation of surrounding tissues. In the ordinary capture process, however, since only gamma rays are emitted, there is little possibility of selective irradiation thereby. Moreover, the radioactivity induced by neutrons in most elements in tissue is very small. In fact, tests in this laboratory and elsewhere have shown that the radioactivity acquired by tissues during an exposure to neutrons greater than that used in most experiments is negligible as far as biological effects are concerned.



In summary, although neutrons may (i) be elastically scattered, (ii) be inelastically scattered, (iii) produce disintegrations, or (iv) be captured, practically all of the ionization produced in tissue by fast neutrons can be accounted for as the result of elastic collisions with hydrogen, carbon, and oxygen nuclei. The small percentage of inelastic collisions that do occur for carbon and oxygen nuclei also result in recoil nuclei, but they are a little less energetic than for elastic collisions. Although disintegrations of nitrogen occur to a small extent, the resultant particle is a proton already prevalent from process (i). The capture process causes some gamma radiation, but in most instances this gamma radiation is much less than that from the source of neutrons itself. Even then, it can be shown that the major share of the ionization is caused by fast neutrons and not gamma rays. The radioactivity resulting in tissue from neutron capture is small and unimportant in producing biological effects.

*The ionization produced in tissue and the role of ion density.—*

In studying the biological effects of neutron rays it is quite natural that their effects be compared with those obtained with x-rays, for a great deal is already known about the biological and therapeutic action of the latter. Any differences between the biological action of the two radiations would have to result either from a quantitative difference in the amounts of energy expended by the radiations in the biological material or from a qualitative difference in the manner in which the same amount of energy is expended in the two cases. Comparative measurements of the amounts of energy expended by the radiations (exposures and dosages) will be considered in a separate section. Now, having just discussed how neutrons lose energy, we can portray qualitatively the comparative manner in which energy is expended in tissue by neutrons and by x-rays.

From a knowledge of the approximate atomic composition of tissue and the energy absorbing properties of the nuclei of these atoms, it can be calculated that for fast neutron irradiation of an average soft tissue, roughly 92 per cent of the absorbed energy is given to recoil protons, 2 per cent to recoil carbon nuclei, and 5 per cent to recoil oxygen nuclei (the balance of 1 per cent resulting from other causes). X-rays interact only with electrons so that in the case of x-irradiation of tissue only high speed electrons result. We need therefore only to compare the expenditure of energy by secondary recoil nuclei with that by secondary electrons.



Swiftly moving charged particles expend energy not only in ionizing atoms and molecules but also in "exciting" them (the raising of electrons to higher energy levels in atoms or the greater agitation of atoms in molecules). In the ionization process an electron is removed from an atom, leaving it a positively charged ion, while the electron becomes attached to some neighboring atom to form a negatively charged ion, the final result being called an "ion pair." On the average a particle expends thirty-two electron volts of energy for every ion pair it creates in air. Since to pull an electron from a molecule in air only about one half this amount of energy is required, the other half must be spent in excitation processes. The average energy spent in producing an ion pair in tissue cannot be directly measured, but it is probably considerably lower than for air; also the fraction spent in excitation probably remains about one half. Although the initial changes in the atoms and molecules whose alterations finally result in biological effect may be brought about by excited atoms or molecules, the biological action is generally attributed to the ion pairs, because of the ability of their charges to initiate chemical and physical change. Also we may focus our attention on the ion pairs produced, because they are the object of most of the measurements used for quantitating exposures, and their quantity represents an approximately constant fraction of the total energy expenditure. Nevertheless, it is to be remembered that the ion pairs are not the only agent capable of initiating biological change (light and heat without producing ion pairs produce similar changes to those of ionizing radiations in some cases).

The density with which ion pairs are produced by an ionizing particle along its path depends on the magnitude of its charge and its speed. For the average quality of the radiations we are considering, the density of ion pairs per cm. of path (specific ionization) produced by electrons, protons, and recoil oxygen nuclei in tissue will be roughly  $10^6$ ,  $10^7$ , and  $10^8$  respectively. The average specific ionization along secondary proton paths can thus be considered to be roughly one hundred times greater, and for the heavier recoil nuclei as much as one thousand times greater, than that along secondary electron paths. Thus, if ion spacing is a significant factor in influencing the biological effectiveness (energy expenditure required for a given effect), or the type of result obtained, differences should appear when the biological effects of



fast neutrons and x-rays are compared. This will indeed be seen to be the case in the discussion of the biological investigations.

Evidence obtained from the use of alpha particles and extremely low voltage x-rays has also shown the biological significance of the spacing of ion pairs. For example, Zirkle (5) in experiments previous to those with neutrons had shown, by using a very small organism which could be placed so as to intercept different regions of the paths of alpha particles for which the density of ion pairs were different, that the biological effectiveness per ion pair increased considerably with increase of the specific ionization in this region of large ion pair density. More recently Zirkle (7) has found that the role of the linear energy absorption (specific ionization) along the paths of ionizing particles is not the same for all organisms, the effectiveness of the radiation per unit dose may increase sharply, increase very little, and even decrease significantly with increase in the specific ionization. This is consistent with a biological effectiveness of neutrons as compared with x-rays that is different for different organisms. Lea, Haines & Coulson (8) made an extensive series of measurements on the lethal action on bacteria of radiations covering a wide range of ion densities (alpha, beta, and gamma rays of radium and very soft x-rays). They found that the relative sensitivity of *B. mesentericus* to *E. coli* increased as the specific ionization of the ionizing particles increased.

Experiments using the range of qualities of x-rays generally employed therapeutically have shown no significant biological difference per unit of tissue dose. Since the average specific ionization of the electrons probably is not varied by more than a factor of five and the density of the ion pairs is not in the region where this factor would play an important role, this independence of quality is to be expected. In the experiments of Lea *et al.* (9), only a small difference in the relative sensitivities was found between very energetic gamma rays and x-rays of only a few kilovolts.

It might be assumed that by administering x-rays in very intense short exposures an effect of increased density of ion pairs could be observed. However, to decrease the random average spacing of ions produced throughout a volume by the random paths of secondaries until it is as small as that along the individual electron paths themselves ( $10^{-5}$  cm. apart) would require instan-



taneous shots of several thousand roentgens. To produce a random spacing of ions, with x-rays as close together as on proton tracks ( $10^{-7}$  cm. apart), would require an instantaneous exposure of one billion roentgens.

It is interesting to picture the same total amount of ionization produced in an organism by fast neutrons and by x-rays. In the latter case the total length of paths will be a hundred times greater than in the former. There will thus be one hundred tenuous electron paths with x-rays for every heavy proton path with neutron rays. The average distance between ion pairs on the electron paths will be about  $10^{-5}$  cm., so that an electron may pass several hundreds of water molecules or scores of protein molecules without producing an ion pair. On the proton paths, however, the average distance of ion pairs apart will be only about  $10^{-7}$  cm., so that a proton may produce an ion pair every few water molecules apart or one or more ion pairs in nearly every protein molecule traversed. A heavier recoil nucleus would ionize practically every water molecule it passed and produce many ion pairs in a protein molecule, but there would be only about one of such paths for every ten proton paths or one thousand electron paths.

#### MEASUREMENT OF THE QUANTITY OF RADIATION

It is important in considering the quantity of radiation used in biological and radiological work to distinguish between "exposure" and "tissue dose." Let us reserve the term "exposure" for the physical quantity of radiation to which the biological material is exposed, that is, the amount applied. Then by "tissue dose" we shall mean the amount of the biologically effective agent produced in the irradiated material, that is, some quantity in the tissue related to the radiation absorbed, or for brevity, the amount absorbed. The term "dose" is quite generally used for what we here are calling "exposure," but when thus used, it is in the sense of "applied dose." The term "tissue dose" is then used for the absorbed quantity. However, more clarity can be maintained in differentiating between the quantities if "dose" is used only when "tissue dose," or absorbed quantity, is implied.

There is, of course, a direct relationship between the two quantities because the same amount will always be absorbed from a given amount applied, if the character of the radiation and the absorbing material is not changed. The relation can be



stated thus: The exposure multiplied by an absorption factor, which depends on the character of the radiation and the irradiated material (often also on immediately surrounding material), equals the amount absorbed, or the dose. It is important to make this distinction between exposure and dose because the absorption factor relating the two varies with the radiation and the material used. Consequently, the same exposure with different radiations or materials does not always result in the same amount absorbed in the material.

*Exposures.*—It is often convenient to measure exposures in terms of an arbitrary unit which may be any quantity that will allow accurately reproducible exposures. For example, the milli-ampere-minutes of cathode ray current is a unit that has often been used for x-ray apparatus. As long as the output of the apparatus stays constant the number of milliamperes-minutes will determine exposure values reproducibly. The constancy of output could be checked by any sufficiently accurate physical, chemical, or biological test. For radium, a constant source, millicurie-hours is a convenient unit. In the case of the cyclotron the current of deuterons that hits the target being bombarded is integrated in microampere-hours by a meter. Under constant conditions exposures can be then taken directly proportional to the micro-ampere-hours of bombardment. The neutron exposure delivered by the cyclotron, with a given irradiation arrangement, can also be integrated by measuring the radioactivity induced by the neutrons in a suitably chosen indicator. In the earliest biological exposures with neutrons a standard sized layer of sulphur was placed in a given position during each exposure. The amount of radioactive phosphorus of fourteen days half-life produced in the sulphur during an irradiation is directly proportional to the number of incident neutrons. Integration by this means was independent of fluctuations of target current prevalent in the early work. For investigations of the effects of slow neutrons the radioactivity induced in gold or manganese has proved useful under constant irradiation conditions for integrating exposures.

A very satisfactory means of measuring exposures of fast neutrons is to use the method now widely used for x-rays, i.e., integration of the ionization produced in a thimble chamber by a condenser type  $r$ -meter. The condenser-chamber unit can be detached and exposed to the radiation without the necessity of continued observation by (proximity of) the experimenter. Since



the reading obtained at the end of an exposure is an integration, errors due to fluctuations in the radiation intensity are avoided. The total ionization that occurs in the thimble chamber will be proportional to the total flux of neutrons that has passed through it, hence to the total exposure. In this laboratory, a standard Victoreen  $r$ -meter with a 100  $r$  condenser-chamber is used. The unit of fast neutron exposure is arbitrarily taken as that amount which produces the same reading with this meter as a roentgen of x-ray. Thus an  $n$  of fast neutrons produces inside this 100  $r$  Victoreen thimble chamber the same amount of ionization as is produced by an  $r$  of x-rays. In tissue, however, the amount of ionization produced by these two exposures is not the same. The ratio of the tissue doses can be fairly well approximated in several ways as will be discussed shortly.

Through the use of consistent and accurate measurements of exposure, even though arbitrary in preliminary work, a great deal of information can be gained. Survival curves and other relations of effect versus exposure can be compared for different organisms and materials. The influence of changes in physical or physiological conditions or in time factors on the sensitivity to radiation can be studied. Pertinent examples will be found in the literature and in the results to be discussed later. However, while discussing the subject of exposure and dosage measurements, let us consider the manner in which comparisons were made in this laboratory (see Table I, p. 43) of the sensitivities of different biological objects relative to each other both with neutrons and with x-rays.

The character of each radiation was maintained constant throughout a particular set of comparisons, and material was chosen for which the irradiation arrangements were comparable (small objects of similar composition). For each radiation the exposures then remained on the same basis. Each exposure was integrated by an ionization chamber or other consistent means of integration. The condition of the irradiated material was controlled and, whenever possible, was divided into lots (neutron, x-ray, and control) and treated simultaneously so that sampling of material and time factors would be uniform. It is found that the relative sensitivities of different biological objects for neutrons are not the same as for x-rays, that is, when the number of  $r$  to produce certain effects are recorded, the number of  $n$  to produce these same effects do not parallel the  $r$  values. If the  $n$  unit were



any other arbitrary value than that chosen (say twice or one half as large) the fact that the values of  $n$  and  $r$  are not parallel (do not have a constant ratio) would not be altered. Thus an arbitrary unit suffices to show the different relative sensitivities for the two radiations.

*Tissue dose.*—The same fact (the nonparallel relative sensitivities of the objects in  $n$  and  $r$ ) when viewed from the standpoint of the relative exposures ( $r/n$ ) for each object means that the comparative effects of x-rays and neutrons are not quantitatively the same for all objects. Since the ratios of the exposures ( $r/n$ ) are different for different biological effects, the question arises whether the ratios of the doses are also not the same, that is, whether a different expenditure of energy in the tissues is required for the effect with neutrons than is the case with x-rays.

This question can be answered without actually having to determine how much tissue dose is produced in each case. Suppose that  $r$  units of x-ray exposure and  $n$  units of neutron exposure are required to produce a given effect, and that  $k_x$  and  $k_n$  are respectively the absorption factors relating dose to exposure for the two radiations, then from the previously stated relation  $E_x = k_x r$  and  $E_n = k_n n$ . Then  $E_x/E_n = k_x/k_n (r/n)$ . The absorption factors for different biological materials will be nearly constant for each radiation, consequently their ratio may be assumed a constant,  $K$  (which is not unity). Thus  $E_x/E_n = Kr/n$ . Expressed in words this means that for tissues of comparable absorption the ratios of tissue doses for the two radiations are directly proportional to the ratios of exposures. Since  $r/n$  is not the same for all the objects tested, it follows that  $E_x/E_n$  is also not the same for all objects. Even if x-rays and neutrons were equally effective per unit of absorbed energy for one object ( $E_x = E_n$ ), for another object with a different ratio of  $r/n$ , different amounts of energy would be required. Thus not only in terms of exposures ( $r/n$ ), but also in terms of tissue doses ( $E_x/E_n$ ), neutrons are shown to have quantitatively different effects as compared with x-rays.

Although the measurement of neutron exposures in arbitrary units is satisfactory for the experiments referred to, there is need for a standard or even an absolute unit. With a standard unit, different workers could compare exposures on the same basis. With an absolute unit based on energy absorption, changes in quality of the radiation would not affect the dosage values. A standard unit could be based, for example, on the ionization



produced in a small thimble-type chamber of a specified composition and a primary standard could be preserved somewhere. The difficulty is to find a universally reproducible standard, as well as one whose response is affected as little as possible by changes in the energy of the neutrons or by the gamma rays that accompany the neutrons. Victoreen thimble chambers though standardized for x-rays have neutron responses that differ (however, not usually as much as 20 per cent). For the present status of neutron biology, such differences are not serious. For example, when the  $n$  unit used by Zirkle & Lampe was checked against the one used in this laboratory, less than 10 per cent difference was found.

It is better, however, to adopt as a standard a certain amount of ionization realizable in a manner independent of a particular kind of ionization chamber, that is, a standard based on some absolute quantity which is a constant of nature and always reproducible. The roentgen, the accepted unit of x-ray exposure, is now based on an absolute value. It is that quantity of x-radiation which produces 1. e.s.u. of charge of one sign along the paths in air of all the secondary electrons originating, as a result of the irradiation, from 1 cc. of N.T.P. air. It is possible to realize this measurement with different kinds of chambers, though the parallel plate, open air type is the most satisfactory throughout a large range of qualities. As so defined the roentgen is in reality proportional to the amount of energy absorbed from the radiation by a specified mass of air (about 85 ergs per gram of air per roentgen). This choice has proved to be a fortunate one for x-rays (and for gamma rays with proper precautions) because, as pointed out by Mayneord (10), the energy absorption per unit mass in soft tissues closely parallels that per unit mass of air for both x-radiation and gamma radiation. Consequently, a roentgen of exposure (energy expended per unit mass of air) produces very nearly the same biological dose (energy expended per unit mass of tissue) throughout the range of qualities that are generally feasible to use for therapy.

This fortunate relationship between the roentgen and tissue dose applies only to a thin layer of tissue for which the degree of penetration of the primary radiation and the absorption of scattered radiation need not be taken into account. In a large mass of tissue, such as a patient under treatment, radiation penetrates into and is scattered about and reabsorbed differently for different



qualities of radiation, in which case the dose at various levels in the body is different per roentgen of exposure with different qualities. However, in small test objects where reabsorption of radiation scattered by the material is negligible, a roentgen will represent practically the same dose for all qualities. An exception would be for cases in which the tissue might contain a greater percentage of heavy elements (sulphur, iodine, calcium, etc.); then the absorption of energy, hence the tissue dose, would be greater per roentgen at softer qualities. Most biological test objects, however, do not have compositions which could account for greater absorption of energy per roentgen. Any differences in biological effect per roentgen for qualities above about 40 kev. x-rays (monochromatic) would have to be ascribed to differences in the ion spacing along electron tracks and not to total energy absorbed. As already pointed out the difference in ion spacing along electron tracks for the different qualities of x-rays in use is not considered great enough to influence the biological effectiveness. A great deal of experimental work has shown no difference in the biological effectiveness per unit of dose in the therapeutically useful range of x-ray qualities. This would mean not only that no quality has quantitatively different effects as compared with any other quality, but that the sensitivities of tissues relative to each other are the same for different qualities. Exceptions might be found for bone, skin, or thyroid gland which, because of their content of heavier elements, could have more absorption at softer qualities.

It is because the light elements in tissue and in air have similar and nearly equal absorption properties for high voltage x-rays that the roentgen has such a desirable relationship with tissue dosage. However, in the case of fast neutrons, tissue (because of its large hydrogen content) absorbs considerably more energy per unit mass than does air. If in the relation between tissue doses ( $E_x/E_n = k_x/k_n \cdot r/n = K \cdot r/n$ ) the exposures  $r$  and  $n$  are both measured in terms of energy absorption in air, the factors  $k_x$  and  $k_n$  are respectively for x-rays and for neutrons the ratio of the energies absorbed per unit mass of tissue and air. As just discussed,  $k_x = 1$  approximately. For neutrons having an energy around 3 mev. it has been calculated as well as determined experimentally (11) that a gram of average tissue absorbs about seven times as much energy as a gram of air, that is,  $k_n = 7$ . In this



case,  $K = 1/7$ . For experiments in which the relative exposures of x-rays and neutrons have been measured by air absorption, the relative tissue doses thus can be approximated by dividing the ratio of exposures by 7. This is done for the results of Gray *et al.* (22). However, there are disadvantages to the adoption of air absorption for a unit of neutron exposure. As it is not known how the relative absorption factor varies with the energy of the neutrons,  $k_n$ , may not be constant with changes in quality as  $k_x$  is for x-rays. Also when gamma rays and slow neutrons accompany the fast neutrons the factor  $k_n = 7$  cannot be applied to the total air absorption because for the gamma ray contribution  $k = 1$  and for slow neutrons  $k$  would be much less than 1 since there is more nitrogen per gram of air than per gram of tissue. In fact, because of the disintegrations in nitrogen, oxygen is a better gas to use than air. In case the radiation is complex as above, the relative absorption factor  $k_n$  must be determined by special physical measurements. A better relationship between exposures and tissue doses is, of course, obtained if the energy absorption measurements can be made in a medium with an absorption approximating that of tissue, for  $k$  would then be nearly constant and equal to 1.

The problem is to measure the energy expenditure in an appropriate tissue-like medium. Since the heating effects of even large exposures are too small for accurate determinations the energy cannot be measured directly. However, as we have discussed, the energy,  $E$ , expended by secondary particles is directly proportional to the ionization,  $I$ , they produce. The relation is stated  $E = IW$ , where  $W$  is the average energy expended by a secondary particle in producing an ion pair in the medium. Although  $W$  is not known accurately for all media, it can be approximated and in any case it will be constant for a given medium. Consequently, a measurement of the value of  $I$  always gives a constant fraction of the value of  $E$ . Since the ionization produced in tissue, or in other liquid or solid media, cannot be collected properly, ionization measurements must be made in gases. For the latter, the measurements can be made quite accurately and conveniently. The ionization produced in a solid or liquid can, however, be determined indirectly by two methods. One is to measure the ionization produced in a gas in a large "wall-less" chamber, that is one in which practically all the ionization results from secondary particles arising from absorption



processes in the gas alone and very little or no ionization results from secondaries ejected from the chamber walls. This we may call a "gas effect" method and the ionization measured is proportional to the energy absorbed by the gas. One must then choose a gas which for the radiation studied has properties of energy absorption effectively the same as the designated medium. The second method is to measure the ionization produced in a very small gas cavity in the designated medium, the conditions being such that practically all the ionization is produced by particles ejected from the walls. In this method, which we may call a "wall effect" method, the ionization is determined mainly by the energy absorption properties of the wall material. Obviously if the absorption properties of the gas and the wall in either method can be chosen equal, the effect of the wall in the "gas effect" method or the effect of the gas in the "wall effect" method can be made unimportant.

One type of "wall-less" chamber is the large parallel plate, open type used for x-ray standardization, but this requires the use of a small, sharply defined beam of radiation in order to define the volume from which ions are collected. For neutrons a fine grid of wires can be used to define a "wall-less" collection volume. The gas itself is then the wall around this volume, and if the volume is sufficient to obtain an equilibrium of secondary particles (that is, has a radius greater than the range of secondaries in the gas) a complete measure can be obtained of the energy expended by the radiation in the gaseous medium. Such measurements have been made for the neutron beam used in many of the biological experiments in this laboratory (12). Some of the problems are: the choice of a gas appropriate for obtaining tissue dose, the separation of the ionization caused by gamma rays and slow neutrons from that by fast neutrons, and the collection of all the ions from the densely ionized paths of the secondaries. A complete discussion is not appropriate here, but, by making measurements of the ionization produced in a large number of gases (especially hydrocarbons) throughout a large range of pressures and strengths of collecting field, results for tissue doses were obtained in agreement with theoretical expectations.

The "wall effect" type of measurements and the conditions for which they validly give an approximation of tissue doses have been extensively discussed and investigated by Gray (13, 14). The ionization produced in thimble chambers with different walls and en-



closed gases have been studied. A measurement independent of the enclosed gas can be obtained by comparing the responses with different gases, with decreasingly small gas volumes, and with decreasing pressures of the gas. Measurements using this method, in this laboratory (15) and by Gray (11), were found to be suitable for approximating tissue doses with neutrons and the results are in agreement.

Both methods, "wall" and "gas" effect, lead to tissue doses for neutrons that are in agreement with each other and with theoretical calculations, but in each case no one measurement or the result with one type of wall or gas alone was sufficient. It was necessary to compare the measurements with walls and gases of varying hydrogen content and interpolate for a medium the composition of tissue. At present one cannot select a simple, single measurement for obtaining tissue doses with neutrons. However, as already discussed we have found the  $n$ , as measured by a Victoreen thimble chamber, to be a convenient exposure unit. From measurements in this laboratory (16) the factor  $k_n$  relating neutron tissue dose to  $n$  exposure has been approximated. A value of approximately 2 is obtained, but because of factors for which it is difficult to allow, the value could be as much as 2.5. In reporting the results the maximum value is assumed. Dividing the  $r/n$  exposure ratio by 2.5 thus gives approximately the ratio of tissue doses with x-rays and neutrons.

#### BIOLOGICAL INVESTIGATIONS

After the preliminary biological experiments, discussed in the introduction, had shown the quantitative differences in the relative effects of neutrons and x-rays on two biological materials, wheat seedlings and the white blood cells of rats, it seemed important to investigate more thoroughly many other biological objects. Consequently, in this laboratory and elsewhere extensive investigations along this line have been carried out, some of the results of which are summarized in Table I. In most of the work the neutrons have been produced by a cyclotron and have been measured with a Victoreen condenser  $r$ -meter as discussed above. The unit of neutron exposure has been the  $n$  which is that amount of neutron radiation which will produce the same reading in the condenser  $r$ -meter as one roentgen of x-rays (Column II). For comparison, most workers have used 200 kv. x-rays, but in some in-



TABLE I  
COMPARATIVE EFFECTS OF NEUTRONS AND X-RAYS

Worker	Biological material	Process studied	I	II	III	IV
			Exposures of x-rays $r$	Exposures of neutrons $n$	Ratios of exposures $r/n$	Ratios of tissue doses, ( $x$ or gamma neutrons)
Axelrod <i>et al.</i> (18)	Mouse tumors <i>in vitro</i>	Inhibition of growth				
	Lympho-sarcoma		2,450	325	7.5	3.0
	Lymphoma		1,700	290	5.8	2.3
	Mammary carcinoma		3,250	525	6.1	2.45
Axelrod (19)	Bacteriophage (staphylococcus)	Inactivation	20,000	11,000	1.8	0.72
Spear <i>et al.</i> (20)	<i>E. Coli</i>	Lethal effect			3.2	1.28
	Mesentericus spores				5.3	2.1
Dempster (21)	<i>Drosophila melanogaster</i> (mutations)	Recessive linked lethal mutations			1.9	0.75
		Gross translocations			3.1	1.24
		Dominant lethal mutations			3.8	1.51
					(77) (11.5 to 22.5)	11.0 2.1 to 3.2
Gray <i>et al.</i> (22)	Bean roots Chick fibroblasts (in tissue culture)					
Lewis (23)	Chick embryo Fibroblasts (in tissue culture)	Inhibition of growth	110,000	55,000	2.0	0.8
Marshak (24)	Horsebean	Per cent abnormal mitosis	65	10	6.5	2.6
	Pea	" "	205	33	6.2	2.5
	Tomato	" "	1,235	190	6.5	2.6
	Mouse sarcoma 180	" "	765	130	5.8	2.3
	Mammary carcinoma Lymphoma					
Zirkle & Lampe (25)	<i>Drosophila</i> eggs	Inhibition of hatching by 50 per cent				
	1½ hours		150	79	1.9	0.76
	4½ hours		745	240	3.1	1.24
	6 hours	Inhibition of growth of root shoot	785	290	2.7	1.08
	Wheat seedlings				6.2 to 11.8 5.9 to 9	2.5 to 4.7 2.4 to 3.6

stances gamma rays have been used, measurements being made in terms of roentgens (Column I). The ratios of effectiveness of neutrons and x-rays have been obtained by dividing the number of roentgens of x-rays and the number of  $n$  of neutrons necessary to produce the same biological effects (Column III). As noted pre-



viously, it is necessary to correct for the relatively greater amount of ionization that neutrons produce in tissue per unit of exposure by dividing the ratio of exposures by a factor which is an approximation of the relative energy expended per gram of tissue by an  $n$  of neutrons and an  $r$  of x-rays (Column IV). The investigations of Axelrod *et al.* (18), Dempster (21), Marshak (24), and Lewis (23) have all been carried out with the sixty-inch Berkeley cyclotron using beryllium bombarded with 16 mev. deuterons and the conditions of irradiation have been standardized in all cases, whereas the work of Gray *et al.* (22) has been carried out with neutrons produced by bombarding deuterium with 2.5 mev. deuterons, and the investigations of Zirkle & Lampe (25) on the Michigan cyclotron were made using 7 mev. deuterons on beryllium. In general the results from the various laboratories throughout the world are in agreement in this one particular: neutrons when compared with x-rays selectively affect some tissues more than others. Because of the fact that the conditions of irradiation and the quality of the neutrons used in the various laboratories have differed somewhat, Table I has been more or less confined to the work of this laboratory, but the conclusions obtained from this work are in general agreement with the results of investigations in the other laboratories, such as of Gray, Mottram, Read & Spear in England (22). Examination of Column 3 shows that the ratios of exposures of neutrons as compared with x-rays vary all the way from 2.1 to 11.8. One can see in Column 4 that the ratios of tissue doses vary from about 0.7 to 11, in general a greater dose of x-rays being required. Although there are evidently considerable quantitative differences, there have not been noted any qualitative differences, as measured by gross and histological changes, in the various cells or tissues (17).

Certain aspects of the investigations of some of these workers should be mentioned. First, it must again be emphasized that varying ratios of effectiveness have been obtained, even to the degree that if one studies the same biological material at different stages of development, different ratios for the same material studied are obtained. For example, in the case of *Drosophila* eggs studied by Zirkle & Lampe (25),  $r/n$  ratios of 1.9 to 2.7 were obtained, depending on the age of the material. These results show that the relative sensitivities of biological materials to neutrons and x-rays are conditioned by the physiological state of the irradiated material. Examination of the work of Marshak (24)



shows that he obtained the same ratios, i.e., about six, whether he was studying the horsebean, the pea, the tomato, or different types of mouse tumors, and his work would not seem to be in agreement with the results of others. However, Marshak studied here the chromosomal abnormalities in these different materials three hours after irradiation. He was studying a single type of biological system in the same stage of cell activity in each instance, and no matter which biological material was studied, the ratio remained the same. This simpler biological change is to be contrasted to more complicated ones such as the lethal effect on bacteria, the inhibition of growth of cells in tissue culture, the inhibition of hatching of *Drosophila* eggs, and the prevention of growth of mouse tumor particles when implanted into mice, after having been irradiated *in vitro*. As a matter of fact, Marshak has recently shown that if he studies the chromosomal abnormalities at different periods after irradiation (corresponding to different stages of cell activity), the ratios do not run parallel. For instance, at twelve hours, the  $r/n$  ratio for the horsebean is fifteen, while that for the lymphoma is nine, these facts showing again that different biological systems vary in relative sensitivity, depending on the system studied and on the physiological state of the particular system.

A further important finding is that different tissues or processes studied in the same organisms also may show different relative neutron to x-ray sensitivities. For example, in the case of wheat seedlings studied by Zirkle & Lampe the  $r/n$  ratio was found to be consistently higher for the root than for the shoot of the same seedlings. Moreover, the ratio depended on the stage of growth after irradiation, though the root and shoot were obviously irradiated simultaneously. Again, as recorded in the table, Dempster (21) observed different  $r/n$  ratios for different mutational processes in the same organism (*Drosophila melanogaster*). The most striking difference is between dominant lethal mutations and recessive sex-linked lethal mutations, neutrons being relatively twice as effective compared with x-rays in producing the former as the latter. In these cases there is little question but what the affected materials received the same doses during exposures since they were integral parts of the same small organisms irradiated homogeneously and simultaneously. Consequently, no tissue dosage arguments are here necessary to show a different quantitative effectiveness, or selective effect, for neutrons as compared with x-rays.

Another question of considerable importance is whether the



shapes of survival curves obtained with neutrons are different from those obtained with x-rays. Although in most cases the survival curves are approximately the same shape for both radiations, several workers (19, 22, 25) have found evidence for a difference so that the question cannot yet be definitely answered for all the material studied.

*Therapeutic use of fast neutrons.*—In view of the fact that neutron rays penetrate deeply into tissue and produce dense loci of ionization there, and also since their relative quantitative effect on various biological materials varies, damaging some tissues to a greater degree than others, the question was immediately asked: Will they have any value in the treatment of cancer and allied diseases? Some of the earlier work (26, 27) with mouse tumors suggested the possibility that neoplastic tissue might be relatively more sensitive to neutrons than normal tissue, but there is no unquestionable method of proving or disproving this possibility in the laboratory, and one immediately looked to the clinic. Consequently in September, 1938 after development of a means of collimating beams of fast neutrons for therapy (28), some preliminary therapeutic tests on patients with inoperable cancer were carried out (29) using the thirty-seven inch cyclotron. A year later the sixty inch cyclotron was operating steadily at intensities sufficient for therapy using a meter treatment distance. The work was then extended so that patients are now regularly treated three days a week with exposures of neutrons in  $n$  approximately one-fourth or one-fifth the exposure of 200 kv. x-rays (in  $r$ ) usually used. R. S. Stone and J. C. Larkin, who are in charge of the work, say that the therapeutic results so far obtained are encouraging. During the past three years 147 selected patients with advanced incurable cancer have been treated. Of these patients, 66 had lesions in the head and neck, 11 in the breast, 17 in the prostate, 3 in the stomach, 6 in the rectum, 4 in the brain, and 16 in other regions. At the present time the duration of the treatment is about twenty-five days, individual treatments being given three times a week, totaling usually about 600 n. Doctors Stone and Larkin have found that 110 n will produce a threshold pigmentation from the fourth to nineteenth day over a  $7 \times 7$  cm. field. It is to be remembered that 550  $r$  of 200 kv. x-rays will produce a similar end result, the reactions being viewed after several weeks in each case. The courses of the reactions, however, seem different. Healing of skin and mucous



membranes after large doses of neutrons seems to be slower than after x-ray injury if a certain limit is exceeded. Neutron radiation sickness and reactions are about like those following x-ray treatment. Of the 119 cases followed, 85 are still living. Much the best group are those with carcinoma of the prostate, since out of a total of 17 cases, 17 are living, 5 of whom were treated over one year ago. These clinical trials are being extended to a larger group of patients, and the early results are very encouraging.

*Therapeutic possibilities with slow neutrons.*—The recent interesting investigations of Kruger (30), relating to the problem of the direct effect of slow neutron rays on neoplastic tissue, are based upon the fact discussed above that when slow neutrons strike boron, they are captured by the boron nucleus, which in turn breaks into two heavy ionizing particles—a helium nucleus (alpha particle) and a lithium nucleus. These two heavy particles travel approximately the diameter of a cell (in opposite directions) and produce ionization even denser than that of protons produced by fast neutron irradiation. One might expect great destruction from this dense, localized ionization which approximates an explosion within the cell. In fact, Kruger has shown that when tumor cells bathed in nontoxic concentrations of boric acid solution are bombarded with slow neutrons, they can be killed with doses of neutrons that are only a fraction of those necessary to kill them directly. These results introduced the possibility that if boron could be localized in neoplastic tissue, one might be able to irradiate these regions with slow neutrons, which would cause localized disintegration of the boron, producing damage only in the neoplastic area and practically none in the surrounding normal tissues. Recently this work has been followed by some experiments of Zahl *et al.* (31) who have been able to get enough colloidal boron or lithium into mouse tumors *in vivo*, so that slow neutrons have inhibited their growth to a greater degree than one would expect from the direct neutron irradiation alone. These results suggest that if methods for localizing boron or lithium in neoplastic tissue can be developed, then it might be possible to treat successfully cancer and allied diseases by whole body irradiation with slow neutrons. If dyes or other compounds containing one of these elements could be found which after intravenous injection would localize in metastatic neoplasms, widespread cancer might be treated with some success.



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WILLIAM H. CROCKER RADIATION LABORATORY  
UNIVERSITY OF CALIFORNIA  
BERKELEY, CALIFORNIA



## PHYSIOLOGICAL ASPECTS OF GENETICS

BY HERLUF H. STRANDSKOV

*Department of Zoology, University of Chicago, Chicago, Illinois*

The two previous contributors to the *Annual Review of Physiology* on the physiological aspects of genetics, Beadle (1) and Sturtevant (2), have appropriately emphasized that all genetics has physiological implications. Hence, material to be summarized in these reviews must be arbitrarily chosen, since not all genetic contributions can be included. Omissions will be many, partly because of lack of space and partly because of inability to cover the entire field. Although we shall not review new genetics books published in the last year, we have listed some at the end of the bibliography.

*Pigmentation.*—No genetic characters lend themselves better to an analysis of the physiological action of genes than do those which are expressed by pigments. This is partly because many genes are known in both plants and animals which affect pigment characters and partly because most pigment genes act directly, that is, intracellularly.

Apparently all pigments of mammals fall into two main series, the dark or melanic and the yellow or xanthic. These are produced in different combinations and in different intensities, depending upon the genetic constitution of the animal in question and also, to some extent, upon the environment.

In guinea pigs seven series of alleles are known which affect skin and eye pigmentation. These are as follows: the *S* series (*S*, *s*), which affects the distribution of pigment over the body surface (animals *ss* are spotted, colored and white); the *E* series (*E*, *e<sup>p</sup>*, *e*), which is responsible for the differential distribution of melanic and xanthic pigments in areas of the fur; the *A* series (*A*, *a*), which affects the distribution of melanic and xanthic pigments in the individual hairs; and four series, the *B* series (*B*, *b*), the *C* series (*C*, *c<sup>k</sup>*, *c<sup>d</sup>*, *c<sup>r</sup>*, *c<sup>a</sup>*), the *F* series (*F*, *f*), and the *P* series (*P*, *p*), all of which affect the intensity of either the melanic or the xanthic pigments or both.

Over a period of years Wright has studied intensively the phenotypic expression of all the possible combinations of these



seven series of alleles of guinea pigs. He has published his results from time to time in various periodicals. We can not discuss all his results here, but we present for reference purposes a summarizing table from Wright (4) of the major effects of some of the gene combinations. The numbers in the table represent intensities of melanin or xanthic pigmentation, graded according to an arbitrary scale.

TABLE 1

THE AVERAGE CONCENTRATIONS OF PIGMENT IN THE HAIR OF GUINEA PIGS AT BIRTH

The sepia and browns are given on a scale in which intense black (EPBC) is 100. The yellows are given on a scale in which intense yellow (eFC) is 100. The latter actually has only about 20 per cent as much capacity for reduction of  $\text{KMnO}_4$  as intense black. Replacement of a, assumed above, by A, replaces the sepia, brown or yellow of E-combinations by the yellow of the corresponding e-combinations in a subterminal band in dark hair. There is no effect in e-combinations. The recessives are here represented by single symbols except in the C—series.

	SEPIA		BROWN		YELLOW			EYE COLOR (E, e; F, f WITHOUT EFFECT)		
	EFPB EIPB	EFpB	EFpB EIPb	EFpb	EfpB Efpb	eFPB eFPb eFpb	efPB efPb efpb	PB	Pb	pB pb
C—	100	21	50	17	6	100	36	Black	Brown	Pink
c <sup>k</sup> c <sup>k</sup>	90	18	42	15	0	38	5	Black	Brown	Pink
c <sup>k</sup> c <sup>d</sup>	82	15	47	13	0	41	5	Black	Brown	Pink
c <sup>d</sup> c <sup>d</sup>	64	9	40	11	0	38	5	Black	Brown	Pink
c <sup>k</sup> c <sup>r</sup>	94	14	43	13	0	19	0+	Black	Brown	Pink
c <sup>k</sup> c <sup>a</sup>	73	9	37	11	0	18	0+	Black	Brown	Pink
c <sup>d</sup> c <sup>r</sup>	75	7	44	7	0	14	0+	Black	Brown	Pink
c <sup>d</sup> c <sup>a</sup>	40	5	31	6	0	14	0+	Black	Brown	Pink
c <sup>r</sup> c <sup>r</sup>	84	5	45	6	0	0	0	Dark red	Dark brown red	Pink
c <sup>r</sup> c <sup>a</sup>	46	1	33	1	0	0	0	Light red	Light brown red	Pink
c <sup>a</sup> c <sup>a</sup>	0	0	0	0	0	0	0	Pink	Pink	Pink



To account for the results of his breeding experiments Wright (3, 4) has formulated an intricate system of gene action and interaction. It assumes substrates upon which enzymes act at various times and places, giving the final pigment intensity and combination. The different enzymes are assumed to be the result of the presence of one or another of the different genes of the seven series of alleles. To arrive at his scheme, Wright tried out many different rate constants. The final scheme, which is reproduced in Figure 1, gives, according to Wright, "reasonably good agreement with the observed quantitative relation in all factor combinations."

It would be extremely desirable to discuss all the details of Wright's hypothesis, but this cannot be done in this review. For details see Wright (3, 4). Before leaving the topic, however, it might not be inappropriate to point out and emphasize that the system does show beautifully the powerful tool which breeding experiments alone can be in an analysis of some physiological processes.

Some biochemical analyses of mammalian pigmentation have also been made. Both the dark or melanic and the yellow or xanthic pigments belong to the group known as melanins. Melanins apparently are derived from tyrosine or its related substance, dopa (dihydroxyphenylalanine) acted upon by oxidative enzymes. According to Bloch, (4a), tyrosine gives dopa as one of its products of metabolism, some of which is oxidized to melanin by the specific enzyme dopaoxidase, and the remainder is converted to epinephrine.

Various techniques have been developed to demonstrate the presence of dopaoxidase in the skin of mammals and to determine its relative amounts in different genotypes. One has been to subject frozen sections of skin to buffered solutions of dopa. Schultz (4b) and Kröning (4c) were among the first to use this method. Russell (5) found that histological sections of guinea pig skin taken from colored genotypes turn dark when immersed for three hours in buffered dopa at a pH of 7.4 and a temperature of 40°C. The darkening occurs only in the cells in which pigment is normally laid down. The intensity depends upon the genotype. If tyrosine is used, no reaction is observed. Russell's work corroborates the view that the coat-color genes of mammals exert their influence through an enzyme system or several such systems which react



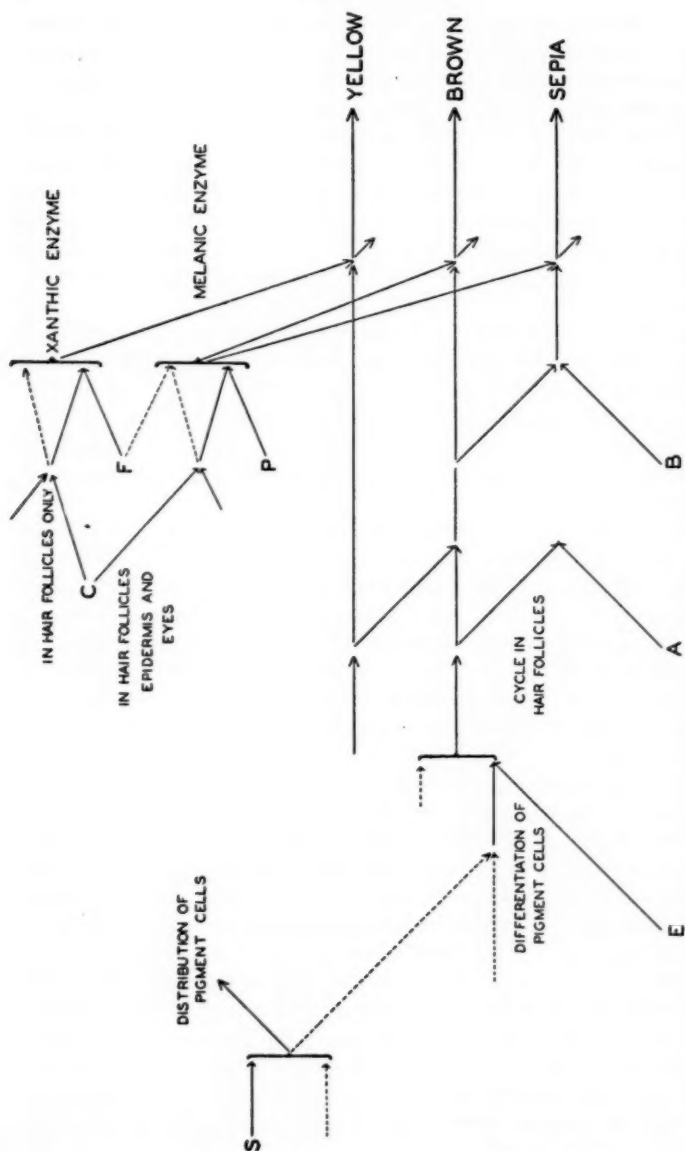


FIG. 1.—A quantitatively possible interpretation of the relations between the actions of certain genes of the guinea pig and the production of melanin pigment



differentially upon melanogens already in the cells. Daneel & Schaumann (6), working with rabbits, found that it was possible to prepare an extract from the skins of deeply pigmented animals which reacts with dopa but not with tyrosine. Beadle (1) has reviewed the other important aspects of the work of these investigators.

Mather & North (7) discuss the method by which the gene "umbrous" presumably acts in the house mouse. This gene is a modifier of agouti and has no effect on nonagouti animals. It produces a greater darkening effect in the homozygous than in the heterozygous condition. The authors conclude that the gene acts by controlling the rate of the darkening reaction.

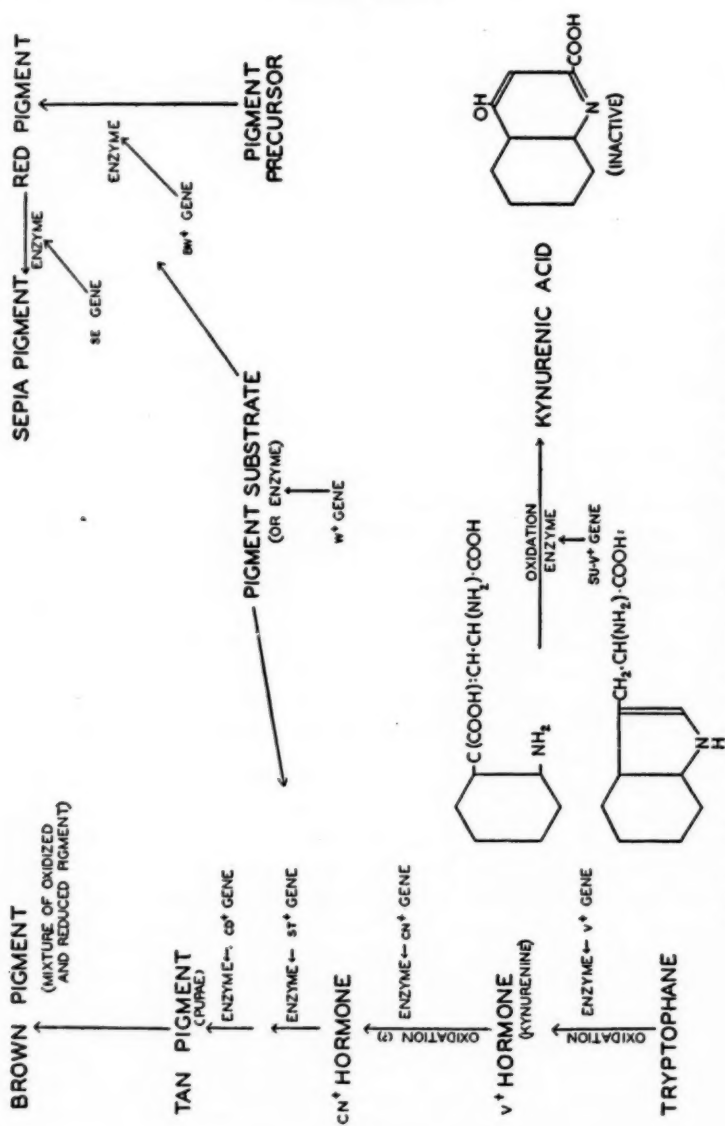
The physiology of pigmentation among invertebrates has also been studied in considerable detail. In fact, these studies have reached a somewhat finer degree of biochemical analysis than have the mammalian studies.

The normal eye color of *Drosophila* is a brownish red. It is known from breeding experiments that different eye colors of this fly can be produced by substituting the recessive alleles of a number of gene loci for the normal dominant ones. For instance, by substituting the recessive allele of the brown locus for the normal dominant allele, a brown eye is produced; by substituting the recessive allele of any one of the vermilion, cinnabar, scarlet, and cardinal loci for the corresponding normal dominant gene, the respective eye color is produced; and by substituting the ultimate recessive allele of the white locus for the normal dominant allele, a white eye is produced.

Biochemical analyses have shown that two pigments exist in *Drosophila*. The one is a red, water-soluble substance which is yellow in acid and red in an alkaline solution. The other is a brown, water-insoluble pigment which is yellow when oxidized and red when reduced. Very little is known regarding the formation of red pigment, but considerable information is at hand regarding the formation of the brown. The latter apparently is derived from tryptophane. When oxidized it gives a substance which has been called the  $v^+$  hormone, and which now has been identified as kynurenine. Kynurenine apparently is converted into the  $cn^+$  hormone, which in turn is converted into the brown pigment.

On the basis of the breeding, transplantation, and biochemical studies which have been made, Beadle (8) and Beadle & Tatum (9)



Fig. 2.—Scheme of assumed steps in the formation of eye pigment in *Drosophila*



have developed a scheme to account for the formation of the various eye colors of *Drosophila* which have been mentioned. Their latest scheme, which appears in the latter article, is reproduced in Figure 2.

According to the scheme shown in Figure 2, normal red eye color of *Drosophila* is a mixture of the red and the brown pigments referred to above. The production of red pigment is under the influence of the genes of the brown locus. In the presence of the normal dominant allele of the locus ( $bw^+$ ) an enzyme is produced which converts the red pigment precursor into red pigment. Consequently, in the presence of all the other normal eye color genes, the eye is the normal red color, a mixture of red and brown. In the presence of the recessive brown allele ( $bw$ ) no enzyme is produced, and consequently, no red pigment is produced, and the eye is brown.

The production of brown pigment according to the scheme is under the influence of the alleles at the vermilion, cinnabar, scarlet, and cardinal loci. The normal dominant allele of the vermilion locus produces an enzyme which converts tryptophane into kynurenine. In the presence of the recessive allele, this reaction goes on to a lesser extent; less kynurenine is formed, less brown pigment is produced, and hence, the eye has a brighter red or vermilion color. There is a recessive gene ( $su-v$ ) which suppresses the action of the recessive vermilion gene. The supposition is that the normal dominant allele of this gene ( $su-v^+$ ) normally converts some of the kynurenine into inactive kynurenic acid. In the presence of the recessive allele ( $su-v$ ) this reaction goes on to a lesser degree, and hence, the normal amount of kynurenine is available to be converted into brown pigment. Consequently, the eye of the homozygous recessive vermilion, instead of being vermilion, as expected, is normal red. The conversion of kynurenine into  $cn^+$  hormone is under the influence of the genes of the cinnabar locus. In the presence of the normal dominant cinnabar allele ( $cn^+$ ) an enzyme is produced which brings about this conversion, but in the presence of the recessive allele ( $cn$ ) this does not occur. As a result, less brown pigment is produced, and the eye is a brighter red or cinnabar. The genes of the scarlet and cardinal loci play a similar role in the conversion of  $cn^+$  hormone to brown pigment.

The genes of the white locus apparently play a role in the production of both brown and red pigment because in the presence



of the ultimate recessive white allele, neither is formed. This fact has suggested to Beadle & Tatum a common step in the formation of brown and red pigments. They write as follows:

This inference is based on our faith in the unproved assumption that a given gene has a single primary action. It may be that the white gene is concerned with the formation of a substrate common to the two pigments, or it may control the production of an enzyme catalyzing basically similar reactions in the two parallel reaction chains.

Regarding the whole system, the authors write

... throughout the scheme we have indicated genes acting through the intermediation of enzymes. In a sense this is a purely gratuitous assumption, for we have no direct knowledge of the enzyme system involved. Since, however, we know that in any such system of biological reactions, enzymes must be concerned in the catalysis of the various steps, and since we are convinced by the accumulating evidence that the specificity of genes is of approximately the same order as that of enzymes, we are strongly biased in favor of the assumption. In this we make no claim to originality, for it has many times been suggested by geneticists that there may be a close relation between genes and enzymes. It is, of course, possible that the immediate products of many genes may be enzymes or their protein components. At the present time, however, the facts at our disposal probably do not justify the elaboration of hypotheses based on this assumption.

Beadle (1) has summarized the early work on the genetics and chemistry of plant pigmentation. We call attention here only to the recent articles by Beale, Price & Scott-Moncrief (10) and by Beale (11).

*Polyploidy and haploidy.*—Until recent years, the study of polyploidy has been limited by the paucity of available material, especially animal material. Plant materials could be found in considerable abundance in nature. It is almost possible now to produce polyploids at will in the laboratory, and a voluminous and detailed literature, too vast to be summarized in its entirety in this review, has grown up around the subject. Blakeslee (12) has summarized the recent work on plants. Fankhauser (13) and Griffiths (14) have succeeded in changing the chromosome number of several species of amphibia by exposing eggs to cold temperatures ranging from 0° to 3°C. Triploid larvae were obtained from such eggs. The authors believe that they produced diploid eggs by inhibiting the second maturation division, which is not completed until one hour after the egg is laid. The triploid cells of the larvae were above normal in size, but the larvae themselves were not. This suggests a low total cell number. Polyploid invertebrates



(with the exception of the silk moth *Bombyx*) usually show gigantism. Lack of gigantism in the cases reported above may be due either to a lower rate of division of the polyploid cells or to a smaller number of cells being present in the embryo at the end of cleavage. Kaylor (15) obtained haploid salamanders by removing the nuclei from eggs before fertilization. The eggs were then allowed to develop with only the male set of chromosomes present. Most of the larvae which developed to an advanced stage were haploid and edematous, as were some haploid larvae obtained by Fankhauser and by Griffiths. It was not possible to relieve the edema by manipulating the salt concentration of the medium. Two triploid larvae were obtained, and contrary to the results which have been discussed above, these were larger than normal.

*Immunology and serology.*—The genetics of certain immunological and serological reactions is well known and has had considerable practical significance. Recently, new techniques and intensive studies have added much to this area of knowledge. By using immune isolysins, Ferguson (16) has demonstrated seven distinct heritable antigens in the red blood cells of cattle. Each cellular substance was recognizable as a single character by its reaction with a specific antiserum or reagent. In genetic tests five of the cellular components behaved as unit characters. The other two were too rare to permit statements regarding their inheritance. Ferguson conjectured that there may be as many blood groups among cattle as there are chromosomes. It is the belief of some medical investigators (17) that the application of refined techniques to man may extend the number of distinguishable human blood groups. The recent discovery by Landsteiner & Wiener (18) of a *Macacus rhesus* antigen (Rh) in some human bloods lends weight to this possibility. Levine, Katzin & Burnham (19) have obtained evidence suggesting that the production of an isolysin against the paternal Rh factor may be involved etiologically in eclampsia, repeated abortion, icterus gravis neonatorum, and erythroblastalis fetalis.

Of interest in connection with the genetics and physiology of human blood groups are the studies which demonstrate the isolation from secreta and excreta of complex carbohydrates with A-specific and B-specific activity. As is well known, the presence or absence of one or both of these substances is under the control of genes. Several investigators have isolated the A-specific carbo-



hydrate. The isolation of B-specific carbohydrate from human blood was first reported by Hallauer (19a). Kin (20) isolated a B-specific carbohydrate-like substance from saliva. Witebsky & Klendshoj (21) have obtained a similar substance from human gastric juice. Although O blood does not possess either isoagglutinin A or B, it is known that beef sera will agglutinate O cells more than the cells of A or B blood from which the A and B isoagglutinogens have been removed. This indicates the presence of some antigen in O blood. Witebsky & Klendshoj (22) have reported the isolation of a carbohydrate-like O-specific substance from the gastric juice of individuals belonging to blood group O. Added to beef sera it inhibits the agglutination of O cells by such sera, this fact indicating that the anti-O antibodies have been depleted. With the isolation and availability of A- and B-specific substances it seems probable that O blood can be neutralized and used more safely for all transfusions. Witebsky, Klendshoj & Swanson (23, 24) find that a few milligrams of A- and B-specific substances will neutralize 500 cc. of O blood. Witebsky & Klendshoj (25) also report over one hundred clinically satisfactory transfusions with neutralized O blood to patients belonging to groups AB, A, and B. They, however, warn that even after neutralization of O blood by A- and B-specific substances there still remain many possible sources of transfusion reactions.

The capacity to develop immunological reactions seems to have a genetic basis. Wheeler, Sawin & Stuart (26, 27) have found that the ability of rabbits to form anti-A and possibly also anti-M sera against human erythrocytes is inherited as a simple Mendelian character. The ability of swine to resist *Brucella* infection is another such characteristic with a possible genetic basis. Cameron, Gregory & Hughes (28) classified pigs that were the progeny of sows and boars resistant to *Brucella suis* infection as resistant, susceptible, and undetermined, depending on high or low agglutination titer. The lymph glands and spleen of all three classes were cultured, and extracts from each were injected into guinea pigs. Almost no evidence of infection could be obtained for the resistant swine, but *Brucella suis* was isolated from three out of four of the susceptible pigs, while one out of three pigs of the undetermined group gave positive results.

Roberts, Severens & Card (29) found that pullorum disease in the domestic fowl usually attacks only chicks with a low number



of lymphocytes. They conclude that the difference between resistant and susceptible chickens is due to an inherited differential in the lymphocyte concentration immediately after hatching. This is the time of greatest susceptibility to pullorum disease.

*Genes in development.*—Neel (30) has analyzed the interaction of the hairy, polychaetoid, and hairy-wing genes in *Drosophila*. He found that all possible combinations of these mutants reduce femur length. The effects of each combination upon the chaetal characteristics was in most instances greater than the sum of their separate effects. This was not true, however, with respect to their effect on the teeth of the sex-comb. Polychaetoid and hairy separately behave as recessives and produce no effect in the heterozygous condition, but their simultaneous heterozygous combination produces an effect which deviates from the wild type. Waddington (31) studied the effects of thirty-eight mutant genes which affect wing development in *Drosophila*. He subdivided the normal course of development into sixteen distinct stages and was able to show that each gene operates at a different stage. Braun (32) related the rate of development to the degree of effectiveness of several mutant genes in *Drosophila*. He found that if the rate is slowed down by starvation, the expression of the mutant is exaggerated. He expresses the opinion that the increased effect might merely be due to the fact that the gene is given more time in which to act. Landauer (33) has described a semilethal gene in birds which acts by shortening the upper beak and the long bones of the extremities. The mutation is an autosomal recessive which allows only thirteen per cent of the homozygotes to hatch. The degrees of shortening of the long bones and of the beak are variable and uncorrelated. Strandskov (34) compared the skeletal elements of two nearly isogenic strains of guinea pigs and found differences which may be attributed to hereditary factors. He presents evidence that some of the genes for body size and shape act as general growth factors and some as specific factors, acting on local parts. Green (35) analyzed skeletal variations in the highly inbred Bagg albino stock of mice for genetic and nongenetic factors. His apportionment of the factors causing variability in the position of the sacrum of this stock was as follows:

Sex factors or factors associated with sex account for 9 to 9.5 per cent of the total; non-genetic factors common to litters, for 8 to 9.5 per cent; other non-genetic factors specific within the individuals, for 80 to 83 per cent.



These results show the necessity for keeping the nongenetic factors in mind, but they in no way negate the findings which show genetic influences. Green & McNutt (36) have described the inheritance of bifurcated xiphisternum in the house mouse. This character invariably segregates with the gene which determines short ears and is probably due to it. This gene is also known to have associated with it decreased vigor (37), changes in size of the cranial bones and a neuromuscular kinkiness of the tail (38), and a smaller body size (39). The effects are believed to be due to an alteration of the early embryonic processes causing both generalized and local retardations in growth. Chase & Chase (40) have described an anophthalmic strain of mice of which 90 per cent of the adults are completely eyeless. Examination of the timed embryos showed that the gene or genes act by inhibiting the optic vesicle after it is formed, thus preventing it from forming a large eyecup. Usually a small cup forms, but it is generally too far from the surface to induce a lens. Anophthalmic adults lack eye remnants and ocular muscles, but have normal lids, orbits, and conjunctivas, as well as large lacrimal glands. The genetic effects are entirely inhibitory, not degenerative.

The expression of a genetic trait often depends upon an environmental threshold. Where the genetic determination of such a response is complex and variable, the threshold may be different for different individuals. Glass (41) apparently encountered such a case in a strain of harelip mice. He found that if antuitrin G is injected into a pregnant female of a harelip strain, an increased percentage of harelip occurs among the offspring.

The genetic factors controlling the normal development of the mature individual are often overlooked, partly because they are difficult to test. A recent study by Silberberg & Silberberg (42) bearing on this point indicates that for mice, at least, the age changes of bones and joints are under genetic control. Inbred strains show consistent differences in the rates of ageing that are often quite marked. The difference between the rate of skeletal ageing in males and females also varies between strains. Many of these differences are true only in a statistical sense.

Studies on behavior are strongly indicative of various definite hereditary components. Male mice of inbred strains show fairly consistent differences in fighting behavior. Rats also show differential susceptibility to convulsions. Maier & Glazer (43) have



tested the latter situation and conclude that the neurotic pattern in rats may be inherited, possibly as a dominant unit trait.

*Sex.*—Ever since 1930, when Unterberger suggested that an increase in the proportion of male births could be produced by douching the female with sodium bicarbonate prior to coitus, there has been a lively interest in the subject of controlling sex in man. Some have claimed that a girl or a boy could be produced at will by use of an acid or an alkali. Cole, Waletzky & Shackelford (44) tried to substantiate these claims in experiments with rats and rabbits. They obtained negative results. Quisenberry & Chandiramani (45) also obtained negative results using rats, but a slight departure from normal in the expected direction was observed with rabbits. Roberts (46), using rats, claims to have obtained confirmatory results.

Strandskov (47) studied the constancy of the genetic and environmental factors which affect deviation from a fifty-fifty human sex ratio by analyzing the variance of human live birth sex ratios in various populations under varied conditions and over varied periods of time. He found that in a local population such as Chicago the human live birth sex ratio does not vary over a period of twenty years more than might be expected due to chance. He found the same to be true for the monthly sex ratios for the United States as a whole. A variance slightly greater than that expected due to chance was found only when the yearly sex ratios of the United States were considered for a relatively long period of time. These results indicate an unusual degree of constancy and uniformity in the physiological effects of these factors.

*Physiology, pathology, and heredity.*—Several heritable physiological and pathological conditions have already been discussed in other connections. Some, however, do not readily fall into the classifications mentioned so far and will be treated separately at this point. According to Cole, Harned & Keeler (48), the tendency towards lowered glucose tolerance is inherited in certain strains of rats. Angioneurotic edema is sometimes hereditary. There is also a nonfamilial variety. Fineman (49) has described and distinguished between the two types. He presents a family of six affected individuals in four generations. The hereditary variety of this condition may be fatal if the glottis or larynx is involved. Recent work suggests that a syndrome characterized by ectodermal dysplasia, hypotrichosis, dystrophy of the nails and teeth,



polydactyly, chondrodysplasia, and congenital morbus cordis may be due to a recessive gene or genes. Richard & van Creveld (50) have tentatively classified this condition as chondroectodermal dysplasia. Askey (51) has emphasized the importance of possible genetic factors in pernicious anemia. The familial incidence of the disease and the data now available regarding this condition in monozygotic twins suggest that pernicious anemia may frequently or even invariably have a hereditary basis. The incidence of anacidity in near relatives of pernicious anemia patients is high. In many instances relatives showing anacidity develop the disease. Idiopathic lipemia is another condition for which a high familial incidence suggests a hereditary basis. Holt, Aylward & Timbres (52) believe that a faulty mechanism for the removal of blood fat by the liver is responsible. Available data on fructosuria have been compiled and analyzed by Lasker (53). Her conclusion is that this condition is an anomaly of sugar metabolism which results in a permanent excretion of fructose. It is extremely rare and quite harmless. Its occurrence is not confined to any age, sex, or racial group. It was formerly thought to be associated with diseases of the liver.

Some evidence for the inheritance of variations in the red blood cell number and other physiological characters of English race horses has been obtained by Patrushev (54). His studies show that the faster animals have a higher concentration of red cells, glutathione, and blood sugar, and a lower index of breathing, pulse, and sedimentation of erythrocytes than do the slower animals. Since speed tends to be inherited in certain blood lines, these high correlations may have significance.

*Genes and endocrines.*—To the geneticist endocrines represent media through which some genes produce their effects; that is, they believe that some genes operate by determining the kind and quantity of hormone that is produced by an organism. What evidence, if any, exists which supports this point of view? Perhaps one of the best examples is the case of the dwarf mouse reported some years ago by Snell and by Smith & MacDowell. This condition is inherited as a simple Mendelian recessive. That the dwarfism is due to a hormone deficiency seems probable. At least, the transplanting of anterior pituitary glands from normal animals to dwarf embryos results in increased size and weight. Of course, this does not prove that the dominant allele of the dwarf gene



locus has a direct role in the chemical production of the pituitary hormone. It could be responsible merely for the normal development of the gland tissue. However, the results are suggestive of a fairly close relationship. DeBeer & Gruneberg (55) have recently published a preliminary note on the histology of the pituitary gland of these dwarf mice. They find that it shows no eosinophil cells in the anterior lobe.

True dwarfism in man is also inherited as a simple Mendelian recessive, and it apparently also represents an example of a gene responsible for a pituitary deficiency. Some attempts have been made to increase the size of such dwarfs by administering antuitrin G. Engelbach & Schaefer (56), Schaefer (57), and Greene & Johnstone (58) report some increase in size above that of a control period.

Further evidence suggestive of differences in endocrine secretion within a species is obtained from morphological studies. Strandskov (59) found striking differences in the size and shape of some of the glands of internal secretion of the guinea pig which are inherited. For instance, the thyroid gland of one inbred strain is thick and compact, whereas that of another is thin and diffuse; and the adrenal of one strain is thick with a well-developed medulla in contrast with that of another in which it is flat with a limited amount of medulla.

All secondary sexual characters of vertebrates probably also represent characters which are affected by genes through the intermediation of hormones. Reports on the effects of hormones on these characters are too numerous and too detailed to be reviewed here. We shall merely call attention to a recent suggestion that some of the characters which we have assumed to be affected by genes through hormone systems are probably affected more directly. At least, the hormones which were formerly assumed to play a role probably play no role at all. We have reference to the assumed effect of hormones from embryonic gonads upon the development of embryonic sex ducts and sex glands. Moore (60) has been able to castrate embryo opossums and has found that the development of the sex ducts and glands proceeds normally in such embryos. This has led him (61) to conclude that in the opossum at least, "sex hormones are not responsible for duct differentiation." Moore's conclusions have a bearing on an explanation of Lillie's freemartin situation. Regarding it, Moore (61) writes



With this in mind, the freemartin effects so beautifully demonstrated by Lillie, and undoubtedly due to humoral substances contributed by the male partner, are conceived of as being brought about by substances produced in the entire organism and not by the gonad.

Thus, from Moore's results it would appear that the sex-determining genes of vertebrates act early in the development of an embryo, not through hormones produced by the gonads, but to some extent more directly, and to some extent through other humoral media.

Genes also produce differences in a given tissue (many of which undoubtedly are fairly direct effects of genes) which make the same tissue in different genetic types respond differently to one and the same hormone. This conclusion is substantiated particularly by the experiments with birds. Among the more recent studies in this area are those of Emmens & Parkes (62, 63) and of Chu (64, 65). It is also substantiated by the differences in the response of the same tissue in the two sexes of a given species to a given hormone. Moore (60) has emphasized this point in his studies on the opossum. He found that the homologous ducts in the male and female opossum embryos, at a stage prior to the time hormones are produced by their gonads, respond differently to the administration of androgens. Presumably these early sex differences in the homologous ducts are determined more or less directly by genes.

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DEPARTMENT OF ZOOLOGY  
UNIVERSITY OF CHICAGO  
CHICAGO, ILLINOIS



## DEVELOPMENTAL PHYSIOLOGY

BY HOWARD L. HAMILTON AND B. H. WILLIER

*Department of Biology, The Johns Hopkins University,  
Baltimore, Maryland*

Each new individual has its beginning in protoplasm of a specific genetic constitution. How such basic organized material produces the form and function of the embryo is the outstanding problem of embryology. Development from the egg consists of a progressive elaboration of interrelated systems, whose various constituent processes involve (a) the action of the genes, (b) interactions between embryonic parts (action and reaction or "correlative differentiation") through such agents as morphogenetic stimuli, hormones, nerve stimuli, etc., and (c) the action of external environment (oxygen, temperature, etc.). Finally (d) each particular process produces a specific new physiological substratum in which a succeeding event or process takes place and so on until the parts and functions of the embryo are fully established. All of these processes are accompanied by metabolic changes in the embryo or its parts which are themselves indices of the nature of the differentiation processes.

In this review an attempt is made to put together the results presented in the literature in such a way as to give emphasis to the main problems of development.

### ORGANIZATION OF THE EGG

The protoplasmic ground substance of the egg contains an array of chemical substances, the arrangement of which determines to a considerable extent the future orientation of embryonic parts. When this arrangement is experimentally disturbed by external agents, then corresponding alterations are produced in the symmetry of the embryo. In addition to the factors which he has already found to determine polarity in the *Fucus* egg, Whitaker (1) reports that unilateral radiation with ultraviolet light causes the rhizoids to form on the halves of the eggs away from the source of the illumination. Pease (2) has used other artificially-induced gradients to study the determination of bilateral symmetry. Certain chemical gradients determined the bilateral plane in *Dendras-*



ter eggs so that the least inhibited side became ventral. The fixation of symmetry was not necessarily associated with differential inhibition of cleavage, and, because of the chemicals which were effective, he suggests that the key enzyme system in bilateral determination is the cyanide-sensitive respiratory system. The bilateral plane, as well as the polar and developmental axes, could be shifted in *Cumingia* and *Chaetopterus* (3) by centrifuging the eggs, presumably because spindle movements were restricted by the packing of egg inclusions. In the frog, it is claimed that directed rotation of orientation will establish the plane of bilateral symmetry in any desired position independent of the point of sperm entrance (4, 5, 6).

Several attempts have been made to find the location of organ-specific substances in the egg cytoplasm by centrifuging eggs, but the results have been more a confirmation of the existence of such substances rather than a precise explanation of how they arise or their mode of integration. When eggs of *Ciona* were centrifuged before fertilization, the tissues and organs which subsequently developed were often displaced from their normal positions (7). Neural tissue was evidently not dependent upon contact with notochord or any other tissue for its differentiation. However, some organs, such as adhesive papillae, were always associated with endoderm, which suggests that their formation is evoked in the ectoderm by the endoderm. E. B. Harvey (8, 9, 10) in her studies on merogony in *Arbacia* found that unfertilized eggs which were separated by centrifugation into nucleated white halves and nonnucleated red halves yielded small, normal plutei from both fragments when these were fertilized. The red merogone could even be activated parthenogenetically and developed as far as a ciliated blastula. If the egg was fertilized before being centrifuged, the white half developed only to the blastula stage and the red merogone failed to develop at all. High centrifugal force broke the egg into halves before it had time to stratify completely; red halves thus obtained developed much better (both fertilized and parthenogenetic merogones), since they contained some of all the materials in the original egg except the nucleus.

The blue color produced by the indophenol reaction has been used by Lehmann (11) on *Tubifex* eggs to trace the origin of the pole plasm, its movements, and localization in the germ bands.

*Physicochemical changes.*—Evidence of the importance of cy-



toplasmic organization for normal development is provided by experiments on aged eggs. Zimmerman & Rugh (12) find that aging frog eggs undergo vacuolization, complete diffusion of pigment, and, finally, dissolution or loss of nuclear components. Nuclear integrity evidently outlasts that of the cytoplasm, and its loss is probably caused by breakdown of cytoplasmic organization. Similarly, Zorzoli & Rugh (13) find that the integrity of the egg cortex is radically affected; when stimulated parthenogenetically, aged eggs show a higher percentage of cleavage than fresh ones, but fewer of them gastrulate. According to Briggs (14), embryos which develop from aged eggs show a tendency to form abnormal nodules of tissue. The deleterious effects of aging could be combated in the clam egg (15) by treatment with calcium, magnesium, egg albumen, gum arabic, and bacteria. Schechter claims that these agents increase longevity by delaying the accumulation of calcium in the egg cortex. In the rat (16), if fertilization is delayed beyond ten hours after ovulation, sterility is increased, litter size is decreased, and the frequency of resorption indicates that many abnormal embryos were produced.

The importance of calcium in the egg cortex is indicated by Wilbur (17) in a study of the activation of *Nereis* eggs by citrates and oxalates. The breakdown of the germinal vesicle and the formation of polar bodies were stimulated by citrates, oxalates, and potassium chloride, in certain concentrations, but if too much citrate was used no stimulation occurred. This is attributed to removal of calcium from the cortex of the egg. Activation also occurred (18) when *Nereis* eggs were irradiated with light in the presence of rose bengal. However, nuclear breakdown was markedly reduced when calcium was removed by treating with citrate solutions. These results support Heilbrunn's theory that calcium must be present in the cortical protoplasm before a cell can respond to ordinary types of stimulation. That the site of the activating reaction is superficial, i.e., in the cortical layer of the egg, is indicated by Lillie's results on the starfish (19). Activation was markedly increased if the eggs were treated with a hypertonic solution for as brief a period as one minute before addition of butyric acid in sea water. The velocity of the activation reaction appears to depend on the water content of the cortical region and the rate of diffusion of reactants in this region. The disappearance of red pigment granules in the *Arbacia* egg when pressure or shearing



forces are applied is interpreted as due to a release of bound calcium from the cortex; the free ions then react with the pigment, causing its breakdown (20). Harvey & Shapiro (21) describe some of the physical properties ("relaxation") of the cortex of eggs which have been deformed. Rounding up of unfertilized eggs as well as the cleavage rate of fertilized eggs is slowed by the presence of calcium ions in the sea water (22).

Henshaw (23) finds that x-radiation of *Arbacia* gametes tends to delay the first cleavage, especially prophase. Zygotes were more sensitive before the fusion of pronuclei than afterwards. Since multipolar mitosis was frequent, it seems likely that radiation causes cell death by producing accessory asters, resulting in an abnormal distribution of chromosomes at mitosis.

Pincus (24, 25) finds that normally fertilized rabbit ova cleave at normal rates *in vitro* in serum or plasma cultures, but that blastocyst expansion does not occur at the normal rate. Growth was improved by adding sulfhydryl compounds to the medium but was completely inhibited by nitrogen or cyanide. These results show that mammalian ova depend on their aerobic carbohydrate metabolism for growth, and he suggests that sulfhydryl compounds act either as coenzymes to respiratory enzymes or reduce a growth-promoting material metabolized by the respiratory enzymes.

The usual array of abnormalities has been produced by treating embryos with chemicals. These include colchicine-induced anomalies in *Drosophila* anatomy which resemble gene effects (26), modifications of cleavage rate by salt solutions and malformations of the embryo in fish (27) and amphibia (28), and inhibition of morphogenesis or destruction of the anterior end of the nervous system in chick embryos by injecting them with solutions of lead chloride (29) or tetanus toxin (30). Copenhaver & Detwiler (31) treated *Amblystoma* eggs with one of the synthetic plant growth hormones (indolebutyric acid). No effect was obtained except with strong concentrations, which increased mortality, retarded development, and produced malformations in the surviving cases.

*Fields and gradients.*—Burr (32) has again raised the question of whether electrical currents determine morphological patterns or whether they are merely an index of an inherent pattern of organization in the protoplasmic ground substance. By measuring the potential difference between animal pole and equator of the am-



phibian egg, he claims that the longitudinal axis of the future embryo can be predicted even in unfertilized eggs, and in subsequent stages after fertilization, because of the greater voltage drop. His conclusion, however, seems still unproved that the "electrical pattern is primary and in some measure at least determines the morphological pattern." For example, Gray (33) was unable to get any differences in the morphogenesis of chick embryos when they were treated with direct currents.

According to the developmental arrest theory, one-egg twins are produced by a division of the primary embryonic axial field caused by a retardation in early development. Newman (34) describes fifteen new double and triple chick embryos which support this theory rather than the idea that twinning is due to a fusion of two embryonic axes resulting from double gastrulation.

With respect to the double gradient system in echinoderm eggs, Hörstadius & Strömberg (35) found that respiratory stimulants (pyocyanin and sodium pyruvate) were animalizing, whereas respiratory inhibitors (potassium cyanide) were vegetalizing. With carbon monoxide treatment, animal halves were more strongly animalized, vegetal halves more strongly vegetalized. Likewise, Lindahl (36) found that the greater the depression of respiration by lithium, the more pronounced was the degree of vegetalization. Lactic, formic, and acetic acids enhanced the lithium effect. An assortment of inhibitions of one or the other gradient with resulting abnormalities was produced when *Dendraster* eggs were treated with sodium thiocyanate, the extent and type of the inhibition depending on the concentration of chemical and whether it was used before or after fertilization (37). To interpret any of these results as indicating an effect on any specific type of metabolism seems premature. It is clear that inhibitions of general metabolism, as shown by the depression in respiration, depress the animal gradient more than the vegetal. The gradient system is not reflected in the oxygen consumption *per se*, however, for it is the same for both animal and vegetal halves and is affected the same way in either half by lithium chloride, potassium cyanide, glyceraldehyde, and pyocyanin (38).

*Axiation.*—The experiments of Swett (39, 40, 41) on axiation in amphibian limbs show that dorsoventral polarity becomes fixed at a later time than anteroposterior polarity. Tissue from the dorsal portion of the limb field is most important for the regeneration



of the limb, and is responsible for fixation of dorsoventral polarity. Fixation of polarity in ear primordia has been studied by Hall (42).

A comprehensive review and summary of these problems of protoplasmic organization is provided in Child's recent book (43). He presents a thought-provoking analysis of the origin and nature of developmental patterns of an individual organism. Such patterns at any moment in development consist of graded activities and behavior in protoplasts of specific genetic constitution and are realized in relation and reaction to environmental factors.

#### DEVELOPMENT OF FORM

With the conversion of the blastula into a gastrula, morphogenesis *sensu stricto* is begun. The mechanics of this process, which are still enigmatic, were attacked by Moore (44), using sugar solutions to balance invagination pressure. It is clear that the infolding cells, either in a gastrula or a neurula, undergo a change in shape (i.e., they become wedge- or flask-shaped). However, his postulate of "contractile processes near the periphery of the blastocoel wall" as a cause of the change in shape may have to be clarified in terms of Schmitt's concept of intersurface action.

The increase in density of amphibian embryos during neurula stages is attributed by Brown (45) to a collapse of the archenteron which squeezes out fluid into the perivitelline space. Since the released substances do not escape through the vitelline membrane, it is suggested that the resulting osmotic activity causes expansion and rupture of the membrane. In contrast to this mechanism in amphibia, hatching of sea urchin blastulae is apparently due to release of an enzyme which dissolves the fertilization membrane [Kopac (46)].

The location of prospective organ areas in the *Axolotl* egg at the beginning of gastrulation has been mapped by Pasteels (47). However, the equilibrium between these areas (with respect to quantity) can be altered by ultraviolet irradiation (48, 49). For example the ratio of amount of chorda to somite material is enlarged by a short exposure, but diminished by long irradiation with ultraviolet light. Spratt (50) has made a rather thorough analysis of the organization of the eye-forming area in early chick blastoderms. If a piece containing the whole area was isolated *in vitro* and divided into right and left halves or anterior and posterior parts,



each fourth developed as though it were part of the whole, with little or no regulation, and the ability to form corresponding portions of the forebrain increased with age. In contrast to this restricted potency of the eye-forming area, the remainder of the blastoderm, after extirpation of the area, regenerated a normal forebrain (with eye), but the ability to regenerate decreased with age. Mikami (51) has studied the development of the eye in urodeles with special reference to the origin of pairedness. Lillie & Wang (52) showed that the feather papilla is a particularly valuable object for studying embryological processes. The dorsal half of the papilla contains the rhachis-forming area. Papillae preserve their innate bilateral organization and their tract specificity in whatever orientation or location they are placed. Twin feathers are produced by bisection and structural chimeras by fusing halves of dissimilar papillae. Other morphogenetic studies include those of Stief (53) on the skin glands of amphibians, and Waterman (54) on the differentiation of kidney tissue in grafts to the rabbit omentum. The origin of sympathetic ganglia in the chick has been traced by Jones (55) to the ventral portion of the neural tube, but additional cases are needed to clinch his argument.

#### EFFECTS OF GENES AND CYTOPLASM

With respect to the regulation of development by different combinations of genes, the subject may be conveniently divided into the relation of genetic constitution to differentiation and the effects of polyploidy. Braun (56) found that reductions in the wing venation of *Drosophila* could be produced by burning small holes in the developing pupal wings. Experiments on different plexus stocks (supernumerary veins) showed that there was a correlation between the amount and sequence of reduction of different elements of extra venation. He suggests that the operation inhibits a general process of vein formation and that a destructive factor may have to be present in the genotype in order for shape changes to take place [but see Waddington (56a) for a contrary view]. The nondependence of the Creeper phenotype in fowl on agents carried in the blood circulation or on general growth inhibitors has been admirably demonstrated by Hamburger (57). When limb buds of homozygous and heterozygous Creepers were transplanted to normal embryos, they showed typical Creeper characteristics in spite



of the fact that the transplants were supplied with normal nutritive material and normal hormones throughout their differentiation. The favored hypothesis is that the Creeper gene causes some deficiency in a general metabolic or respiratory mechanism.

Polyploidy (and haploidy) in amphibians have been produced by refrigeration (58), pricking (59), and by removing the female nucleus immediately after fertilization (60). Triploidy is apparently caused by inhibition of the second maturation division, since cold treatment is effective only during the first half hour after fertilization (58). The individual cells of triploid animals are larger, but there are fewer of them, so that the size of the animal is identical with diploids. Degeneration of the germ cells in the primordial gonads is reported for triploids (59). Haploids are dwarfed and more or less edematous (58, 60). The latter condition could not be reduced by treating the larvae with salt solutions (60).

The possibility of differential sex determination has been revived by a report that X- and Y-sperm could be separated with an effectiveness of 78 per cent by an electric current (61). A preponderance of females resulted from the anode sperm; males, from the cathode.

Wright's recent review (62) summarizes the role of genes in the control of growth, individual and species specificity, enzyme differences, and chain reactions in developmental processes.

The relative roles of cytoplasm and nucleus in development have been studied in amphibia by making hybrid crosses and by studying the behavior of sperm nuclei in androgenetic hybrids. Rate of cleavage is apparently under maternal (cytoplasmic) control at least up to the neural plate stage (63) and the relative sizes of the head primordium and other axial structures are also influenced by the cytoplasm (64). Nuclear differences in hybrids, however, can compensate for the cytoplasmic differences to some extent. When several sperm nuclei enter the same egg (in the absence of an egg nucleus) they vary greatly in their capacities for dividing to form normal mitotic figures (65). Apparently, the dominant sperm nucleus (or in normal fertilization, the diploid mitotic system) restricts the rival sperm to a monaster cycle, so that only a single mitotic system occurs in each egg. If one sperm nucleus fails to gain dominance, then multiple asters arise and an irregular distribution of chromosomes follows, with resulting developmental disturbances.



## ORIGIN OF PIGMENTATION PATTERN

Pigment cells are particularly good material for investigations on the differentiation process and factors which affect it, because they contain a visible intracellular indicator (viz., melanin) of their activity. The origin of melanophores in birds and mammals from the neural crest has been conclusively demonstrated by Ris (66) and Rawles (67). Hamilton (68) finds that the number of melanophores which differentiate and their viability depend on their genetic constitution. White-feathered birds possess fewer melanophores, and these die before they have time to lay down enough pigment to color the plumage appreciably. Melanophores are extremely sensitive to any adverse environmental conditions (68). This accounts for their degeneration in chorioallantoic grafts (69), when the grafts are poorly vascularized, and for the fact that they are destroyed by x-rays (70, 71) sooner than other cells of the feather germ, so that regenerating feathers are white after such treatment. Hamilton (72, 73) also finds that red melanophores usually require the presence of sex hormones (or possibly other sterols) for their differentiation *in vitro* and that the formation of melanin in both red and black melanophores may be catalyzed or inhibited by particular hormones. Willier (74) has shown that physiological factors within the feather follicle, with indices such as rates of growth, time of emergence, etc., influence the differentiation and activity of melanophores. His analysis stresses the interaction of melanophores and feather germ to produce a given feather color pattern, and interprets the data on this problem.

In amphibians, similar actions of the epidermis on the differentiation of melanophores (75) and on the formation of an adepidermal melanophore network (76) are reported. Baltzer (77) obtained chimeric patterns of melanophores in tadpoles by transplanting neural crest material from anuran to urodele neurulae. The donor melanophores maintained their species-specificity (size, intensity of pigment, ability to migrate, etc.) but their topographical distribution into patterns was under host control. Moreover, donor melanophores gradually disappeared as development progressed, until only the host melanophores remained in late larval stages. These results are strikingly similar to those obtained by Willier & Rawles (78) with the melanophores of birds.

Temperature is also a factor influencing pigmentation in in-



sects (79, 80), the usual effect being a reduction of black pigment with increased temperature.

#### CORRELATIVE DIFFERENTIATION: EMBRYONIC INDUCTION

Barth (81) reports that gastrula ectoderm will form neural tubes in the absence of organizer. The frequency of neural differentiation was greatest in large explants and in those which were taken from or near the animal pole region, and was increased if the anteroposterior axis of the explant was maintained. Thus, there is a gradient in neural differentiation of decreasing intensity from the animal pole to the ventral epidermis. These results, though highly suggestive, could be made conclusive by culturing the "neural" material until unmistakable neural structures (e.g., neurones) were formed.

Several new regional inductors have been discovered in amphibians. According to Balinsky (82) the chief factor for the development of the ectodermal invagination of the mouth is induction by the oral endoderm. Schmalhausen (83) and Zwilling (84) find that ear vesicles will develop from prospective ear ectoderm isolated at the premedullary plate stage, and the latter author suggests that they are induced by the roof of the archenteron since neural material is apparently unnecessary. The limb buds of urodeles can serve as inductors of anuran limbs (85). Apparently the inductor emanates from the urodele bud and induces a limb (of anuran type) in the adjacent host tissue. The origin of the lens by induction in *Amblystoma*, just as in other amphibia, has been established by Stone & Dinnean (86). Dalcq (87) describes for *Discoglossus* the peculiar invagination by direct inward immigration of displaced organizer material in its attempts to regulate, and discusses the inductor properties of the chordal anlage and the floor of the blastocoele (88).

Organizer material was again subjected to various degrees of "killing," with the usual result that the more drastic the treatment the less extensive the induction. Thus, nonliving annular cartilage induces tympanic membrane (89) in decreasing amount as it becomes more degenerate. Chuang (90) finds that boiled liver tissue from the mouse or *Triton* first loses its ability to induce mesodermal structures, and finally the capacity to induce ectodermal ones as the boiling is prolonged. On the other hand, Reith (91) reports that



moderate ultraviolet irradiation of inductor material considerably reduces its potency, but that intensive use of ultraviolet causes a return of inductor activity almost equivalent to normal.

The differences in reactivity of ectoderm from various body regions and from different species are discussed by Twitty & Bodenstein (92), Detlaff (93), and Arnold (94).

A clear case of induction in invertebrates is reported by Stern (95, 96) for *Drosophila*. The shape of the testes, whether ellipsoidal or coiled, depends on the vas deferens. The action of the duct to produce coiling seems to be due to the release of a growth-promoting substance in different amounts to opposite sides of the testis. The polar lobe material in the annelid, *Sabellaria*, is thought to be an organizer by Novikoff (97), although it seems more reasonable to call it merely a morphogenetic substance, since its ability to influence development has not been shown to transcend cell boundaries.

The activity of organizers during regeneration is indicated by experiments on the eye and lens. Reimplantation and transplantation of embryonic or adult eyes in *Amblystoma* (98, 99, 100) usually results in an initial degeneration of the retina and lens, followed by regeneration of both (lens from iris) and return of vision. In *Triturus* and the fish, *Fundulus*, slow resorption takes place. Different species of amphibia differ greatly in their capacities for Wolfian lens regeneration (101, 102). Mikami (103) finds that the potency to form lens is greatest in the dorsalmost edge of the iris, although it may be produced by any portion of the upper half of the iris. Humoral factors are apparently involved in lens regeneration, since it occurs most easily in the posterior chamber of the eye, perhaps due to a substance from the retina [see below (104)], and is suppressed by the presence of another regenerating lens, or brain, heart, and liver tissue. If pieces of iris are transplanted to sites other than the orbit (e.g., skin, body cavity), lens formation depends on the place of implantation and the presence of retina (104). In the chick, a humoral substance, which is supposedly located in the crystalline lens and a portion of the retina, inhibits the differentiation of the notochord in regions adjacent to the optic vesicle (105). According to Emerson (106), the regeneration blastema in amphibia can be used with good results as a site for the differentiation of embryonic isolates.



## CORRELATIVE DIFFERENTIATION: HORMONE ACTION

In addition to morphogenetic "hormones" (i.e., inductors), which act through contact with adjacent tissues, there are other substances (the true hormones) which may produce developmental alterations at a distance from their source.

*Sex differentiation.*—The approach to this problem has been almost solely by administering sex hormones to developing animals so as to produce intersexes. In *Amblystoma*, Foote (107) finds that estrogens cause the development of ovaries in genetic males. Testosterone does not have a masculinizing effect on ovaries, although it retards their development [see also Humphrey (108)], but apparently is feminizing since the sex distribution is shifted in the female direction. Other cases of feminization by androgens are reported by van Oordt & Rinkel (109), using dehydroandrosterone on chicks, and by Moore (110), who finds that androgens stimulate the development of Müllerian ducts in the opossum. Other effects in the opossum (comparable to those reported by Burns) are stimulation by androgens of prostate development, male-type phallus, and Wolffian ducts. Estrogen effects include stimulation or distension of both Wolffian and Müllerian ducts, and precocious differentiation of urogenital sinus and male prostate. Differentiation of the prostate, however, can proceed even in the absence of gonads (111). In the terrapin, Risley (112) finds that testosterone stimulates the oviducts as well as typical male structures, and, in addition to its usual feminizing effects, estradiol stimulates the Wolffian ducts. In contrast to these mixed effects, Greene, Burrill & Ivy (113) report that the sex hormones are mutually antagonistic in their effects on the embryonic sexual development of the rat.

By making implants of chick and duck gonad primordia into the embryonic chick coelom, Bradley (114) could show that the undifferentiated gland has the capacity for self-differentiation as to sex. Slight effects of host sex hormones were indicated in the histology of the grafts.

With respect to sex determination in invertebrates, Herbst (115) cites evidence from osmotic studies (using glycerine and butyric acid) in support of his hydration theory of sex determination in *Bonellia*.

Bloch (116) has made a particularly valuable contribution on the physiology of implantation of fertilized ova in mammals. The corpus luteum hormone causes a strong secretion to appear in the



epithelial cells of the uterine endometrium, which, in the mouse, shows regions of increasing and decreasing amounts along the length of the uterine horn. It is assumed that the secretion is absorbed by the blastocysts, providing their first nutrition, and that they implant only in the areas of most intense secretion. Such a mechanism probably accounts for the fact that in the elephant shrew only one embryo develops in each horn of the uterus, because of a very restricted area which will permit implantation, even though each ovary may liberate as many as sixty eggs at a single ovulation (117).

*Hormones in ontogeny.*—Surprisingly enough, the secretion of hormones from a gland may take place before the gland itself has differentiated discrete types of secretory cells. The melanophore-expanding hormone, intermedin, can be detected in the frog, for example, as soon as the hypophyseal primordium is established as an invagination from the buccal ectoderm (118, 119), and in the chick embryo at five days (120) which is before the appearance of definite cell types. Thyrotropic hormone is apparently not produced by the chick pituitary before the eleventh day of incubation, although the thyroid gland is capable of responding to it from one to two days earlier (121). Actual secretion in the thyroid begins at fifty-two days in the fetal pig, at a time when the gland becomes strikingly vascularized (122). Beginning of thyroid function in the frog, as shown by the storing of iodine, begins at the 10 mm. larval stage, just after follicles are formed (123).

*Effects of hormones on cell differentiation.*—In addition to the effects of hormones on melanophore differentiation *in vitro* (72, 73), it is reported that the growth of fibroblasts of the mouse heart is increased by insulin, thyroxine, and low concentrations of estrin, whereas it is inhibited by testosterone, progesterone, epinephrine, cortin, and excess estrin (124). When anterior lobe tissue of the hypophysis and testicular tissue from developing rats are grown together *in vitro*, the hypophysis has a gonadotropic influence on the testis, which involves an increase in interstitial tissue as well as stimulation of spermatogenesis (125). A proliferation of cartilage and retardation of its retrogression, calcification, and ossification was produced in the immature guinea pig by either ovariectomy or injection with progesterone. Aging of the cartilage (as shown by calcification) was produced by administering estrogens or anterior pituitary extract (126, 127, 128, 129).



By using the cornification reaction of epithelia to estrogens as a criterion of their common origin, Burns (130) finds that the neck and trigone of the bladder and the sinus horns originate from the urogenital sinus in the opossum. The sinus epithelium itself is apparently derived at an early stage from the ectodermal cloaca.

*Action during metamorphosis.*—Cytological studies of the pituitary and thyroid glands in normal and starved frog tadpoles, before and during metamorphosis, indicate that starved animals fail to metamorphose because the thyrotropic mechanism [possibly the basophile cells (131)] in the anterior pituitary is impaired, resulting in retention of thyroid gland hormone (132). However, a contrary result is reported by Uyematsu (133), who found that the onset of metamorphosis and formation of limbs are normal in hypophysectomized *Bufo* larvae. A direct action of thyroxine on a metamorphosing structure was obtained by Hartwig (134). When agar blocks soaked in thyroxine were implanted under salamander skin, they caused a local metamorphosis of the larval skin to adult type. Romeis (135) retarded metamorphosis in frog tadpoles by feeding them fresh calf thymus, spleen, or liver. The degree of inhibition is correlated with the amount of thyroid activity: the more inhibited larvae retained a greater amount of colloid in the thyroid gland (136). The result is complicated by the fact that sand and muck substrates in the aquaria tended to abolish the feeding effects. It is somewhat debatable whether thymus actually has any effect, for Gordon, D'Angelo & Charipper (137) could get no obvious hormonal influence on the growth or differentiation of frog tadpoles when thymus gland or its derivatives were injected into them.

The versatility of the thyroid hormone is shown by its ability in low concentrations to accelerate metamorphosis and increase weight in the flour beetle, or to retard growth and development in high dosages (138). The effect was additive in successive generations and possibly inheritable through the female. A counter-versatility was exhibited by tadpoles when their metamorphosis was hastened by injecting them with insect pupation hormone obtained from butterfly larvae and pupae (139).

*Insect hormones.*—The origin of the pupation hormone was traced to the dorsal half of the central brain mass in *Rhodnius* (140) and to the region of the thorax and first two abdominal segments of *Sialis* (141). Its formation in *Ephesia* is inhibited by exposing



the larvae to low temperature (142). The ring gland of *Drosophila* secretes a hormone which causes development of the ovaries (143), and these gonadotropic hormones are qualitatively different in different species (144). Vogt suggests that this may account, in part, for interspecific sterility. Scharrer's excellent review (145) summarizes our knowledge about insect and other invertebrate hormones.

#### NERVE CORRELATION

The trophic role which the nervous system exerts on developing structures is shown by the failure of taste buds to regenerate after nerve section or to differentiate in isolates of embryonic tissue which have no nerve supply (146). According to Schotté & Butler (148), a delicate relationship also exists between the nervous system and the capacity for regeneration. The formation of a regeneration blastema in a urodele limb, for example, involves first a certain amount of cellular dedifferentiation, which is stopped by the establishment of the blastema, and is followed by differentiation of its cells to form a new limb (147). If the blastema is suppressed by either x-rays or ultraviolet light, then extreme dedifferentiation continues unchecked and destroys the stump. Similarly, if the nerve supply to the limb is destroyed, then amputation initiates regressive changes, which continue until the limb is completely resorbed (148). The nerve supply is apparently necessary to check the regressive phase of regeneration and permit the formation of a blastema. In contrast to these neural trophic effects, Etkin (149) finds that the growth and activity of the intermediate lobe of the pituitary are normally restrained by the infundibular nerve tracts, since the pars intermedia becomes enlarged, due to hypertrophy of its cells, either when the gland is grown as an isolate or the infundibulum is partially destroyed.

If groups of neurons (spinal cord fragments) are removed from their normal positions to other parts of the body, then they give off spontaneous rhythmic discharges. Weiss (150, 151) considers this activity to be inherent in all gray matter but held in check by the finer organization of the central nervous system. Humoral factors evidently affect the rate of discharge since the amount of activity fluctuates with the composition of the blood. By using similar transplantation methods, Piatt (152, 153) investigated the problem of nerve-muscle specificity. Since nerves from widely different



sources innervated the same structure, he concludes that directional nerve growth is due to mechanical factors and growth shifts rather than to an affinity of the nerve for a particular muscle.

The development of behavior reactions in amphibia is somewhat more inhibited by low temperature than the development of form, because of a greater retardation of the differentiation of the nervous system than of other tissues (154).

#### MISCELLANEOUS FACTORS

Other more indirect or subtle factors, such as time, mechanical stresses, and even the presence of other tissues, affect the differentiation of cells. In insects, for example, Bodenstein (155) finds that the final size of the adult *Drosophila* eye depends on the length of time during which the eye disc grew in the larva [see also Brehme (156)] as well as on larval nutritive conditions. He also demonstrated that the differences in regulative power between lepidopteran and dipteran leg anlagen are merely differences in time of determination. Thus, the differences are relative just as in "mosaic" and "regulative" eggs (157). A trophic role of larval blood-building cells on the development of wing anlagen in moths is reported (158). According to Evans (159), x-irradiation of grasshopper eggs destroys undifferentiated cells so that the embryo dies. Weiss & Amprino (160) subjected prospective scleral cartilage developing *in vitro* to mechanical tension, with the result that a thin but dense plate was produced. If no tension was applied, or, in the embryo, if the eye was collapsed by puncturing, then the cartilage which developed was thicker and less compact.

The differences between different kinds of tissue with respect to their incompatibility reactions are demonstrated by comparing Milford's results (161) of transplanting embryonic duck metanephros to the chick embryo where no tissue reaction took place, with the extensive incompatibilities obtained by Eastlick (162) in limb grafts made between different birds. Another type of tissue reaction, viz., tissue affinity, can be demonstrated by combining different types of tissue *in vitro* and following their growth and differentiation (e.g., encapsulating reactions) with respect to one another (163). A trophic influence of an organ on the persistence of another of the same kind is reported by Kollros (164) for the urodele balancer.

A redefinition of the terms "self-differentiation," "induction,"



and "self-regulation," and a discussion of the role of each in the development of amphibians, sea urchins, and ascidians is provided in a review by von Ubisch (165). He points out that the capacity of any embryonic isolate to differentiate depends on the composition of its plasmatic milieu, since it determines which and how many of the genes can come into action. Its initial composition, plus whatever changes take place through subsequent action of genes on it, determines how far the process will go. Experimental evidence from ascidians is given for the conversion of one germ layer into another depending on its position in the embryo, and the fixation of fate in germ regions is discussed (166).

#### METABOLISM OF EMBRYOS

*Enzymes.*—Among the many studies on various phases of insect physiology which have come from Bodine's laboratory (167, 168, 169, 170, 171), particular mention may be made of additional information concerning the enzyme tyrosinase. Protyrosinase, from the egg of the grasshopper, which has been activated by excess sodium oleate or Aerosol, will oxidize ascorbic acid in the presence of tyrosine or tyramine (172). The degree of activation exerted by these two activators on protyrosinase is greatly decreased when proteins are added (173). Determinations of kinds of metabolism during morphogenesis by measurement of the R.Q. have been made by Needham *et al.* (174) on the amphibian gastrula, by Öhman (175) on the early development of the sea urchin, and by Schwan (176) on metamorphosing insects (butterflies). A possible relationship between cytochrome oxidase and the division process in *Arbacia* is suggested by Krahle *et al.* (177). Peptidase is evenly distributed throughout the cytoplasm of *Paracentrotus* embryos (178, 179). Respiratory studies of morphogenesis in the chick [Philips (180)] show that there is a hundred-fold increase in oxygen uptake with the beginning of incubation but that the increase is equal for all parts of the blastoderm. The relatively steady increase in oxygen consumption of *Fundulus* eggs during the first few days of development involves almost entirely the cyanide-sensitive portion of the respiration, and can be correlated with increasing cell number and amount of material in the active embryonic mass (181).

Chemical assays have been made of the distribution of ascorbic acid in early chick embryos (182) and of minerals in chick embryo



blood (183), in the developing tooth (184), and in the human amnion and chorion (185) and rat placenta (186).

#### EMBRYONIC ORGAN PHYSIOLOGY

In addition to Huggett's review of fetal nutrition (187), Hogg (188) has followed the correlation of functional capability with the development of sensory nerves in the skin [see also (189) for a discussion of fetal movements], and Windle *et al.* (190) have summarized the changes which occur in the blood during fetal life.

Barry (191) observed that the frequency of heart beat in chick embryos increases up to the fifth day of incubation. The acceleration is rapid at first, but becomes more gradual as development proceeds. An experimental analysis of this "progressive acceleration" (192) suggests that it is caused by a reduction in cardiac distension, due to a deflection of blood into newly-forming arteries.

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DEPARTMENT OF BIOLOGY  
THE JOHNS HOPKINS UNIVERSITY  
BALTIMORE, MARYLAND



## WATER METABOLISM

BY JOHN P. PETERS

*Department of Internal Medicine, Yale University School of Medicine,  
New Haven, Connecticut*

Since water is so universally involved in metabolic processes, but has never been given separate consideration in this journal, it has been necessary to exercise discrimination in the selection of topics for discussion and at the same time to include in the bibliography contributions that antedate the current year. The topics chosen for major consideration are: (a) the distribution of water in the body, its allocation to various compartments of the body, and the forces that determine interchanges between these compartments; (b) the factors—especially endocrine influences—that determine gross exchanges of water with the environment. These seem to the reviewer the provinces of the subject that are at the moment receiving the greatest attention and in which the most significant contributions have been made. Other topics might have been selected: for example, reactions to high temperatures. An increasing interest in the hazards of industry has stimulated activity in this field. But recent investigations seem only to have confirmed earlier work upon the relation of exchange of water and salt to processes of heat dissipation and the compensatory mechanisms that are brought into play.

### BLOOD VOLUME

The technique of measuring plasma volume by means of dyes has been greatly improved by the substitution for other dyes (chiefly red) of T-1824, Evans' blue, and the wider employment of objective photometric methods to estimate its concentration in the serum. Gregersen and his associates have demonstrated that the disturbing effects of hemoglobin, resulting from hemolysis of blood, are eliminated by the use of this dye with proper filters (1, 2) and that the dye neither penetrates nor is absorbed in appreciable quantities by blood cells (3). They have also examined the changes in its concentration in the plasma after intravenous injection. On the basis of these investigations techniques have been devised for both animals and humans, adapted to the spectrophotometer (4, 5) and to Evelyn's photoelectric colorimeter (6).



Essentially, through these studies, procedures have been established by which the volume of fluid over which the dye T-1824 and others with similar characteristics are distributed, can be measured with accuracy. The more fundamental question, whether this volume is identical with that of the circulating plasma, they have completely neglected. It has been demonstrated by Bazett and his associates (7, 8) that, in spite of the introduction of these new techniques, blood volume measured by dyes still exceeds by about 10 per cent measurements made by means of carbon monoxide; these findings confirm the earlier work of Whipple and his group. It is a safe generalization that in the measurement, by dilution methods, of the volume of a body of fluid bounded by membranes of variable permeability, other things being equal, that solute is to be preferred which is least diluted—i.e., is distributed through the smallest volume of fluid. Nevertheless, dyes have been more widely elected than carbon monoxide: first, because the dye methods are technically simpler and lend themselves more easily to repeated measurements; second, because of misgivings that carbon monoxide might find its way into blood cells which were not properly in circulation, but segregated in various repositories, e.g., the spleen or the bone marrow; third, that it might combine with myohemoglobin in the muscles; fourth, that red blood cells, which convey the carbon monoxide, might not be evenly distributed in the circulation. The second and third sources of error it will be noted should give an exaggerated estimate of the blood volume and could not explain the discrepancy between the carbon monoxide and dye methods. The fear that myohemoglobin may absorb carbon monoxide has been largely dispelled by the discovery that myohemoglobin has a far smaller affinity for carbon monoxide than has blood hemoglobin (9, 10). For blood hemoglobin the ratio of the affinities for oxygen and for carbon monoxide is about 200, while that for myohemoglobin is about 15 at body temperature.<sup>1</sup>

Hahn, Balfour, Ross, Bale & Whipple (11) injected into dogs blood from other dogs which had received radioactive iron. This had been incorporated in the hemoglobin within the red blood cells of the donor and thereby served as a label upon these cells. The

<sup>1</sup> These two figures can not be compared precisely because they are not derived from the same species under identical conditions, but they indicate the relative order of magnitude of the oxygen and carbon monoxide affinities of the two compounds.



total red blood cell volume of dogs, as measured by means of the radioactive iron, proved to be only 75 to 80 per cent of the volume estimated from measurement of the plasma volume by the dye method and of the relative cell volume by hematocrit. From these figures it may be calculated that measurements of total blood volume by the two methods differ by about 10 per cent, which agrees well with the discrepancy between the carbon monoxide and dye methods. The volume of circulating cells, measured by radioactive iron, remained constant for a period of one to three days, which seems to preclude in the healthy dog any appreciable interchange of circulating cells with cells which may be immobilized in the bone marrow, spleen, or other repositories.

Ferrebee, Leigh & Berliner (12) have shown that T-1824, when injected, does not remain confined to the blood stream, but also enters thoracic lymph, confirming an earlier observation of Smith about brilliant vital red. Freeman, Freedman & Miller (13) report that in animals in surgical shock large quantities of dye escape from the circulation into the abdominal viscera. Calvin (14) has presented evidence that, in extreme states of asphyxia, dye leaves the blood stream. Gibson & Evans (5) have recognized the errors arising from diffusion of dye into the lymph, but believe they are largely obviated by extrapolation of the "elimination curve" to zero time. Gregersen & Stewart (4) found that the concentration of dye in plasma did not become constant five minutes after injection, as Keith, Rowntree & Geraghty first claimed; instead, they showed that it attained a constant slope only after twenty to thirty minutes. They proposed that the true plasma volume be determined by extrapolation backward along this curve to zero time, an expedient which had been earlier suggested by Sunderman & Austin (15) and others in connection with other dyes. Gilder, Müller & Phillips (16), however, found that the concentration of dye in samples of blood plasma, taken simultaneously from veins of fore and hind limbs, the jugular vein, and sometimes the portal vein of dogs, became uniform within five minutes; this fact indicates that the dye had been evenly distributed throughout the blood stream in this short interval. The concentration did, indeed, continue to fall at a moderate rate for a longer period, before straightening out into the constant "elimination curve," suggesting that the latter part of the so-called mixing curve gave a plasma volume smaller than that estimated by extrapolation on the elimi-



nation curve. The former probably more nearly represents the true plasma volume; but neither can give a correct volume if diffusion into the lymph begins, as it presumably does, immediately after injection of the dye.

Ebert & Stead (17) have called attention to another source of error in dye methods—changes in the optical properties of serum in the course of experimental procedures. Extraction of dye from the plasma into butyl alcohol, which has been advised by Harington, Pochin & Squire (18), may eliminate this difficulty.

Clearly the best of dye methods thus far devised does not measure the volume of the blood plasma. The carbon monoxide method appears to be sounder, even if allowance must be made for unequal distribution of red blood cells within the vascular system, which probably exists, because blood cells at least cannot escape through the walls of the blood vessels with as great facility as dyes. For the measurement of changes of plasma volume in response to physiological disturbances or pathological disorders, dye methods are equally unsuitable, because it is impossible to evaluate the proportion of these changes borne by lymph and blood plasma respectively.

#### LYMPH VOLUME

Recent investigations of lymph flow have revealed that the flow of thoracic duct lymph is increased by measures that augment the quantities of interstitial fluid in the parts of the body that drain into the duct: the administration of saline or water by stomach tube or the injection of saline intravenously, injection of pituitrin (19), injection of histamine (20), reduction of the pressure of oxygen or carbon dioxide in the blood (21). Flow is diminished slightly by injections of mercurpurin (19). It has been demonstrated repeatedly that, when the flow of thoracic duct lymph increases, the quantity of protein in the lymph also increases (20, 21). Dyes used for measurement of plasma volume are restrained by capillary walls, not because of their large molecular size, but because they are adsorbed upon the proteins (1). They therefore provide a means of earmarking the serum proteins, and their escape from the blood vessels into thoracic lymph is presumptive evidence that proteins are also escaping. McCarrell, Thayer & Drinker (22) have proved that the concentration of protein in the lymphatics of the gall bladder and liver, which intercommunicate freely, is the same as that in the serum, verifying earlier observa-



tions. Starling pointed out that, unless it were of this magnitude, a proper fluid exchange could not be maintained in the liver. What proportion of this protein is derived from the blood stream and what proportion originates in the regions drained by the portal lymphatics remains to be ascertained.

From other parts of the circulation dye seems to escape only when some injury or disturbance increases the permeability of the capillaries. Even when the dye was given to dogs in such concentrations that all tissues were stained, Evans & Gibson (23) could detect none in edema fluid, though it appeared in purulent exudate from burns and in albuminous urine. Ferrebee, Leigh & Berliner (12) note that urticarial wheals which developed in one dog were colored by the dye, confirming Govaert's observation that in urticaria and angioneurotic edema the exudate contains protein which escapes from the regional capillaries.

#### EXTRACELLULAR FLUID VOLUME

It has been recognized that a large number of substances, when injected into the blood stream, distribute themselves over approximately the same volume of fluid, which amounts to 20 to 30 per cent of the body weight of animals. Among these substances are sulfocyanate, sulfate, sucrose (24), bromide (25, 26, 27), and magnesium (25). Because this space is of the same general magnitude as the volume through which injected sodium and chloride are distributed (28, 29, 30, 31), it has been inferred that it corresponds roughly with the extracellular fluid of the body, although it is known that most of the substances mentioned are not entirely excluded from all cells. Both sulfocyanate and bromide enter the red blood cells and appear in gastrointestinal secretions (32, 33). Sulfocyanate seems also to be restrained to a small extent by combination with lipoids in the blood plasma (34). When magnesium sulfate is injected the concentration of magnesium in the blood plasma, after an interval, falls more rapidly than that of sulfate, although the former is excreted more rapidly, this fact indicating that magnesium gradually escapes into parts of the body that sulfate can not penetrate (25). Nevertheless, the volumes of distribution of these substances are sufficiently alike to give reasonable assurance that they find their way, in general, into the same fluids of the body and that these must be chiefly extracellular. Sucrose appears to be more completely excluded from cells than any of the other substances; it does not enter the gastrointestinal tract and is



not a normal constituent of the body. It should, therefore, be superior to the other substances mentioned for the measurement of the extracellular fluid. In keeping with this, it appears to give smaller volumes (24). It is, however, excreted in the urine so rapidly that if kidney function is normal, large corrections must be made for the quantities excreted in the urine. For the same reason, it is difficult to insure equilibrium between plasma and extravascular fluids, and measurements can not be repeated at short intervals. Because they are excreted more slowly and because they can be given by mouth, therefore, sulfocyanate and bromide have been preferred, in spite of other disadvantages.

The volume of the extravascular fluids in adult mammals has been estimated at 20 to 30 per cent of the body weight, varying from species to species, and, within any one species, bearing an inverse relation to the proportion of fatty tissue that the animal possesses. Brodie, Friedman & Ferraro (35) have found that in humans the bromide space is more closely correlated with surface area than with weight, probably because reference to this measurement corrects to some extent for differences in the amounts of adipose tissue. They found in male patients a volume of  $10.6 \pm 0.5$  l. per sq. m.; in twenty female patients  $9.4 \pm 0.05$ ; and in fifteen male medical students  $9.7 \pm 0.55$ .

#### TOTAL BODY WATER

To measure the total water in the body some substance must be found that can pass freely all cellular membranes, and that undergoes no chemical combination or alteration. Xylose and creatinine have been suggested; but both seem to be destroyed to some extent in the body. From the standpoint of diffusibility urea is ideal; but it is excreted with great rapidity, is produced in endogenous metabolism, and, under certain circumstances, at least, can be utilized by mammals. It has been used in dogs with apparently satisfactory results by Painter (36). In this animal it has also been suggested that sulfanilamide is suitable. From analyses of whole blood, tissues, and urine of dogs, Marshall, Emerson & Cutting (37) concluded that it was uniformly distributed throughout the water in the bodies of these animals and that it was not chemically altered nor destroyed. Painter (36), acting on this suggestion, found that the total fluid volume of dogs, measured by sulfanilamide, coincided with simultaneous estimation by means of



urea and by direct measurement (weighing the dead dogs before and after desiccation). Like Marshall *et al.*, Painter analyzed whole blood, not plasma. Since there is considerable evidence that sulfanilamide is not equally distributed between cells and plasma of blood, but becomes more concentrated in cells (38), Marshall's & Painter's figures can only mean that it is also far more concentrated in tissue cells than in extracellular fluid. In this case it is not suitable for measurements of water volume and the apparent uniformity of concentration in tissues must be coincidental. In humans or other species which actively acetylate the drug, it is certainly unsuitable for the measurement of body water, because the acetylated fraction is known to be unevenly distributed (38). Purple & Lavietes [cited in (39)] attempted to use thiourea, which appears to be quite as diffusible as urea, is excreted in much the same manner, and can be recovered quantitatively in the urine. Unfortunately, when given in large enough quantities to permit accurate measurement in serum, it provokes severe gastrointestinal symptoms. Before this had been indubitably demonstrated, three measurements were made, one on a patient and two on the investigators, which established the total fluid volume of humans at 68 to 70 per cent of the body weight.

#### EXCHANGES BETWEEN CELLS AND EXTRACELLULAR FLUID

Evidence has steadily accumulated to indicate that the osmotic pressure is uniform throughout the body, in extracellular and intracellular media alike, and in most of the secretions of the body, fully elaborated urine being the most striking exception. It follows that membranes within the organism do not obstruct the passage of water by diffusion and that its relative distribution between intracellular and extracellular media is determined by the relative osmotic pressures of these two phases. In the extracellular phase the osmotic pressure is, in turn, determined chiefly by the concentration of sodium salts. The degree of segregation of the bases in the body and their influence upon movements of water have been more accurately defined. Through the investigations of Darrow and his associates (40), Eichelberger & Hastings (41, 42), and others it has been established that sodium and chloride are largely confined to the extracellular fluids. Muscle cells appear to be particularly free from sodium and chloride. These elements are, however, found in variable concentrations in other tissues, notably the



stomach, intestinal mucosa, and kidneys (43). Sodium is also found in bone and cartilage (44, 45), and chloride in connective tissue (46) and in the central nervous system (43, 47).

This intracellular sodium and chloride appears to be subject to restraints from which the extracellular fraction is free. When radioactive sodium is injected it finds its way relatively slowly into some of the intracellular repositories (48), assuming at first a volume of distribution quite similar to that of sulfocyanate (49, 50). When sodium is added to or removed from the body without an equivalent amount of water, the volume of the space in which sodium is dissolved, estimated from its concentration in the serum, changes to the extent that would be expected if the increment of sodium was all confined to the "extracellular compartment" while osmotic equilibrium with the cells was re-established by an exchange of water (29, 41, 50, 51). Similar shifts of water occur if the osmotic pressure relations between extracellular and cellular compartments are disturbed by alterations of acid-base equilibrium; and again the transfers of water are evidenced by changes of the concentration of sodium and chloride in the extracellular fluid (41). If isotonic solutions of sodium chloride are injected, water, sodium, and chloride behave as if they remained entirely in the extracellular compartment (42, 43). Amberson, Nash, Mulder & Binns (47) reduced the concentration of chloride in the plasma of cats to an extreme degree by perfusing the animals with solutions of sodium sulfate and acacia and by a variety of other methods. In muscle, liver, kidneys, and red blood cells the concentrations of chloride fell *pari passu* with those of plasma in such a manner that the curves relating them, if extrapolated, passed through the origin. This suggests that the chloride in these tissues is in simple diffusion equilibrium with that of blood plasma. Other tissues, however, gave up their chloride less readily; curves from these tissues, when extrapolated, did not pass through the origin, but through a point that indicated that when the plasma became free from chloride the tissues would still contain varying amounts of chloride. This suggests that a variable proportion of the chloride in these tissues is not in diffusion equilibrium with that of the plasma. This fraction corresponds roughly with the fraction that Manery & Hastings (43) and others have attributed to the cells, being greatest in those tissues in which endogenous chloride is most abundant.

From these experiments it is evident that there is little or no



tendency for cells to yield or assume inorganic components to aid in the adjustment of osmotic pressure. This is illustrated also in the less drastic experiments of Mellors, Muntwyler & Mautz (29), and Remington, Parkins & Hays (50). They depleted animals of sodium and chloride by withdrawing fluid from the peritoneal cavity after intraperitoneal injections of glucose, thereafter maintaining the animals for various periods without salt, while permitting them access to water, thus keeping the extracellular fluids in a hypotonic state. From exchanges of sodium and chloride and from the distribution volume of sulfocyanate it was inferred that the intracellular fluids expanded by taking water from the extracellular space and remained in this condition until the animals were again given salt. Potassium and sodium did not appear to escape from the cells to compensate for the sodium lost by the extracellular fluids.

These are only fragments of continually accumulating evidence that intracellular and extracellular electrolytes are not in simple diffusion equilibrium and are not to the same extent under obligation to water. If potassium is given to an animal it is excreted with great celerity, as if it were a foreign body, which indeed it is in the extracellular fluid, which normally contains only the minimal quantities of this element that are necessary to supply the demands of the cells. If additional potassium is given it finds its way temporarily into certain cells (52, 53, 54). At the same time, it seems clear from both chemical analyses (55, 56) and studies with radioactive isotopes (57, 58, 59) that it is not distributed through the tissues in the same proportions as the endogenous potassium and that it is distributed gradually and irregularly over a period of many hours (57, 58). Inorganic phosphate behaves much like potassium, although there are distinct differences in their volumes of distribution and in the rates at which they penetrate various tissues. Although the native magnesium of the body is far more concentrated in cells than in extracellular fluids, injected magnesium escapes from the extracellular space at an extremely slow rate (25, 60), and it is extremely difficult to wash magnesium out of muscle cells (61).

In blood, when the metabolic activity of the cells is reduced to a minimum by chilling, potassium and phosphate do not traverse the membranes of the blood cells in appreciable quantities, even when their concentrations in the serum are greatly increased (62). Ra-



radioactive isotopes of potassium, if added under these conditions, remain entirely confined to the serum (63). If, however, the metabolic activities of the cells are accelerated by warming the blood to body temperature, both potassium and phosphate move into or out of the cells, the direction of their movements depending upon the nature of the cellular metabolic processes (64, 65). Potassium also moves to and from tissue cells in response to certain metabolic activities (66, 67, 68).

In the red blood cell model the transfers of potassium and phosphate may or may not be accompanied by exchanges of water, depending upon the character of the associated metabolic reactions in the cells (69). Some of the transfers involve reciprocal movements of sodium which would obviate the need for exchange of water. In the experiments dealing with the distribution of injected potassium and phosphate, mentioned above, it is impossible to discover any transfers of water than can be attributed to the effect of these ions. However, it is impracticable, because of its toxic effect, to give large enough quantities of potassium to alter osmotic relations greatly. Furthermore, the distribution of injected potassium is a relatively slow process. Destruction or regeneration of cellular protein appears to be accompanied usually by the release or absorption, respectively, of equivalent amounts of water and potassium. These elements seem to be associated in a similar manner with both glycogen and protein in the liver (69, 70, 71). On the other hand, no evidence has been adduced that the excretion or retention of potassium conditions or is conditioned by the volume or salt content of the extracellular fluids. Fenn and his associates (67, 68) have detected escape of potassium from the muscles during activity, the potassium being partly replaced by sodium. Heppel (72) has shown that if animals are deprived of potassium, but provided with sodium salts, the cells will accept sodium as an inferior substitute for potassium. On the other hand, Harrison & Darrow (73, 74) found that potassium increased in the muscles of animals after removal of the adrenals without a proportional increase of water.

These phenomena raise the question whether all the potassium and phosphate in cells is equally unrestrained and osmotically active. Experiments of Solomon, Hald & Peters (75) with blood cells suggest that in these particular cells it may not be, although Rapoport & Guest (76), with the aid of certain assumptions, have



calculated an electrolyte balance between blood cells and serum. Solomon, Hald & Peters found that when blood, hemolyzed with certain precautions, was subjected to ultrafiltration through a simple cellophane membrane, sodium and potassium were not distributed in the same proportions between substrate and filtrate, while the organic phosphate esters were altogether restrained by the membrane.

That potassium may command water has been demonstrated by Eichelberger (77) by analysis of muscle tissue of hydronephrotic dogs after injections of potassium chloride, the potassium of which, in these animals, appears to penetrate the muscle cells. Potassium and phosphate are, however, more responsible to metabolic processes than to conditions of hydration and, compared with sodium and chloride, play relatively minor roles in the disposition or movements of water within the body.

#### ALIMENTARY WATER EXCHANGES

The interchange of fluids and solutes between the alimentary canal and the true *milieu interieur* has been approached chiefly as a problem in membrane equilibrium with little attention to the physical forces that determine the direction of motions of fluid *en masse*. Wells (78) has advanced further evidence that this is controlled by a balance of hydrostatic and colloid osmotic pressures. He finds that the movements are defined by the equation  $(dW/dt) = K(TP - OP_i - IP)$ , in which  $dW/dt$  is the rate at which fluid passes into the intestinal lumen,  $TP$  is the hydrostatic pressure in the capillaries,  $OP_i$  is the osmotic pressure of the colloids in the interstitial fluid of the intestinal villi, and  $IP$  is the hydrostatic pressure within the intestinal lumen. He tested the equation by varying the pressure in the intestinal vessels and in the intestinal lumen.

#### THE EFFECT OF TISSUE PRESSURE OR ELASTICITY ON MOVEMENTS OF FLUID IN THE BODY

The magnitude of tissue pressure or elasticity and its influence upon motions of fluid between blood and tissues has been investigated by new methods. Burch & Sodeman (79), by a direct method, found that the subcutaneous tissue pressure of humans in the recumbent position is 8 to 54 mm. of water. It rises higher than this in the foot with the subject motionless in the upright position,



and is increased by venous stasis. Wells, Youmans & Miller (80) have reported similar values. Intramuscular pressure, the latter observers find, varies somewhat with the character of the muscle, being higher in those that are more tightly covered with fascia, like the anterior tibial, than in the more loosely covered muscles like the gastrocnemius. Intramuscular pressure is extremely responsive to venous stasis and increases greatly during muscular contraction. Evidently the muscles are better protected than subcutaneous tissues against transudation. This has been demonstrated in another manner by Eggleton (51). She found that when, by the injection of water, muscle cells were forced to swell for osmotic reasons, fluid was displaced from the interstitial spaces of the muscular tissue.

#### THE RELATION OF WATER AND SALT TO URINE EXCRETION

Gamble, in his already classical studies of the interrelations of water and electrolytes, advanced the general thesis that the conservative and excretory functions of the kidneys were so attuned that they tended to maintain in the extracellular fluids a constant concentration of sodium and, *ipso facto*, a constant osmotic pressure. Although this general thesis remains unshaken, a new body of conditioning factors has emerged that indicates that the volume of the extracellular fluids may have certain prerogatives. McCance & Widdowson (81) discovered that human subjects, depleted of salt by a combination of sweating and salt deprivation, when given a dose of water, excreted it at an abnormally slow rate, although the water obviously distorted the internal environment more than usual. The same type of reaction is exhibited in the experiments of Remington, Parkins & Hays (50), and Mellors, Muntwyler & Mautz (29), in which animals were depleted of salt by intraperitoneal injections of glucose with subsequent paracentesis, and in those of Holmes (82) in which depletion was effected by means of sucrose. The volume of extracellular fluid in these animals did not diminish in proportion to the salt that was removed, even over long periods, although this necessitated the persistence of a low osmotic pressure in this fluid and consequent swelling of the cells.

Faced with the necessity of readjustment in two dimensions, osmotic pressure and volume, the organism is forced into a compromise in which both functions are partially protected. If the



stimulus which elicits reactions aimed at conservation of volume came from the interstitial spaces themselves, localized edema might be expected to provoke diuresis that would lead to dehydration of the nonedematous portions of the body. The edemas of nephrosis and of malnutrition also would be inexplicable. In protein starvation or following plasmapheresis Weech (83), by indirect measurements, showed that plasma volume diminished, while extracellular volume increased, from the very outset. This has been confirmed by McClure & Hinman (84) by analyses of muscle tissue from rats during the development of nutritional edema. The reduction of glomerular filtration that results from low protein diets may stem from the same cause. Strauss & Fox (85) find that even moderate anemia is attended by a demonstrable retention of fluid. The feature common to all these conditions is diminished blood volume, which was also noted by McCance, Remington *et al.*, Mellors *et al.*, and Holmes in their salt-depleted subjects. This may be the factor responsible for the failure to excrete water in the normal manner.

Certain observations cast doubt upon the propriety of linking water, sodium, and chloride together as inseparable functions, while treating ions at the same time as independent variables. The sodium of sodium sulfate is not treated altogether as the sodium of sodium chloride (25) even by normal kidneys. When sodium sulfate was injected into dogs by Smith, Winkler & Schwartz (25), chloride almost disappeared from the urine, even when enough sodium chloride was administered simultaneously to raise the concentration of chloride in the serum far above normal. Furthermore, chloride excretion was not resumed for a considerable interval after the concentration of sulfate in the urine had begun to fall, although serum chloride continued to rise. Administration of extra sodium chloride only accelerated the elimination of sulfate and exaggerated the hyperchloremia. Serum sodium also rose to excessive heights, despite which the sodium excreted fell short of that given, some ammonium being substituted for it in the urine. Comparable to this is the rapid excretion of potassium when potassium chloride is given, coupled with the fact that the chloride is excreted more rapidly than the chloride of an equivalent amount of the sodium salt. The sacrifice of sodium chloride in the diuresis of glycosuria may compel some modification of the traditional explanation of the dehydrating action of sugars.



The reciprocal obligations of water and electrolytes in the process of excretion is commanding renewed attention (86, 87); the existence of a purely osmotic ceiling to urinary concentration is being questioned. The mutual independence of urea and chloride has been more rigorously demonstrated by Gilman & Kidd (88). The retention of chloride after sulfate injections in the experiments of Smith, Winkler & Schwartz (25), cited above, did not seem to be referable to osmotic limitations because the combined concentrations of sodium, chloride, and sulfate in the urine fell far below their maximum while chloride excretion was still suppressed.

#### ACTION OF ADRENAL CORTICAL HORMONES

The discovery that removal of the adrenals leads to excretion of sodium salts and depletion of sodium in the extracellular fluids, while cortical extract promotes its retention, has given rise to the opinion that the function of the cortical hormone, as far as water and salt metabolism are concerned, is to conserve sodium by promoting its reabsorption in the renal tubules. This may be an oversimplification. Willson & Sunderman (89) found that when the fluid intake of a patient with Addison's disease, who was maintained by provision of extra salt, was restricted, the urinary concentrations of sodium and chloride did not increase as they would have in a normal person. The concentrations of these ions in the serum consequently rose; the patient became dehydrated and weak and required extra water to restore his strength. Swingle, Parkins, Taylor & Hays (90), on the other hand, report that adrenalectomized dogs are peculiarly susceptible to water intoxication. It is, of course, possible, that these phenomena are quite dissociated. The primary effect of adrenalectomy, so far as urine formation is concerned, may be merely to retard reabsorption of sodium salts. Subsequent impairment of the excretion of sodium and salt may depend entirely upon loss of fluid from the blood stream to the extracellular spaces with consequent hemoconcentration. Hemoconcentration was noted by Willson & Sunderman and has been particularly emphasized by Swingle and his associates. Neither the salt depletion nor the hemoconcentration, which characterize adrenal insufficiency, appear to be critically related to the disastrous effects of this condition because improvement is noted in adrenalectomized animals after administration of cortical extracts before any changes in electrolytes or the disposition of



fluid in the body can be detected (91). Conversely, claims that adrenal cortical hormone has a beneficial effect on all conditions of shock and salt depletion should be received with some skepticism. Salt depletion is not a negligible feature of adrenal insufficiency since administration of sodium salts with proper amounts of water will maintain the life of adrenalectomized animals for long periods. Moreover, desoxycorticosterone, which appears to act chiefly by restraining salt wastage and to have little or no effect upon carbohydrate and protein metabolism, has proved an almost complete therapeutic substitute for the adrenal cortical hormone (92, 93, 94).

Ragan, Ferree, Phyfe, Atchley & Loeb have recently reported that this compound, when given to patients with Addison's disease or to adrenalectomized dogs, induces a retention of salt that may become sufficiently great to give rise to edema, accompanied by signs and symptoms of congestive heart failure (95). When given in large doses to normal animals, however, it provokes profuse diuresis with dilute urine (96). The authors believe that the condition differs in certain respects from the diabetes insipidus produced by destruction of the posterior lobe of the pituitary. The polyuria appears to be relatively resistant to the action of posterior pituitary extracts, but can be checked by restriction of fluids. The concentration of sodium in the serum is elevated and rises further when fluids are restricted. The specific gravity of the urine also rises under these conditions. The polyuria is associated with "no significant evidence of dehydration." They suggest that the polyuria may be merely a consequence of excessive thirst. The evidence at present available indicates that, so far as the metabolism of salt and water is concerned, the adrenal cortical hormone—or those elements of the internal secretion of the adrenal cortex which influence salt and water excretion—resembles desoxycorticosterone in its action.

#### THE ACTION OF THE POSTERIOR LOBE OF THE PITUITARY GLAND AND DIABETES INSIPIDUS

Both experimental and clinical data suggest that the anti-diuretic hormone of the posterior lobe of the pituitary gland tends to cause a retention or reabsorption of water in excess of sodium. To this extent its action is opposed to that of the adrenal cortex. The distinctions which Ragan, Ferree *et al.* (96) emphasize



between the effects of desoxycorticosterone and diabetes insipidus may be quantitative rather than qualitative. It has been clearly proven that administration of sodium chloride aggravates the polyuria of diabetes insipidus, although it raises the specific gravity of the urine little, if at all (97, 98). The diuresis can also be reduced, but not eliminated, by limitation of salt or water. In one clinical case, Chu, Liu & Yu (98) found that restriction of water induced hemoconcentration and caused the concentrations of both sodium and chloride in the serum to rise. Serum sodium and chloride also rose when as much as 8 gm. of salt were given daily with only 10 l. of fluid. Neither limitation of fluid nor limitation of salt raised the specific gravity of the urine significantly. In the normal subject or animal, pituitary extract has little effect unless water is given or unless the animal possesses a certain amount of stored water, in which case a part or all of the water is retained, while excretion of salt continues at about the normal rate (99). It is hard to find unequivocal evidence to support the claim that the elimination of sodium and chloride is actually facilitated by pituitrin. By the administration of sufficient water and pituitrin, however, it is possible to increase the volume of water in the body quite definitely and to lower the concentrations of sodium and chloride in the serum (99). Because she found that the inhibition of diuresis by pituitrin was inversely proportional to the amount of water given, Pickford (100) concluded that endogenous secretion of pituitrin is suppressed by the presence in the body of an excessive load of water. There is no reason, however, why the law of diminishing returns should not prevail in this field of physiology, as it does in most others. White & Findley (101) have pointed out that the responses of patients with diabetes insipidus differ from those of normal persons, not in kind, but only in intensity. Chu, Liu & Yu (98) have emphasized the fact that the patient with diabetes insipidus, on any regime, after a period of adjustment, tends to reach a state of relatively stable equilibrium.

The amount of water drunk by either normal dogs or dogs with diabetes insipidus, according to Bellows & Van Wagenen (102) is not affected by removal of the olfactory and trigeminal nerves, while Fisher, Magoun & Hetherington (103) have reported that the thirst of cats with diabetes insipidus can be mitigated by administration of fluid through a stomach tube. These observa-



tions, together with Adolph's (104) studies of dogs with esophageal fistulae prove that, despite subjective impressions, the stimulus to ingestion of fluid does not arise in oral sensations. As proof that polyuria precedes thirst in diabetes insipidus they are less significant than the fact that in this condition restriction of fluid leads to dehydration, and Swann's (105, 106) demonstration that nephrectomy abolishes thirst. The recurrence of polydipsia when salt is given to nephrectomized dogs with diabetes insipidus (106) may be discounted in view of the thirst-provoking effect of such solutions in any condition.

Undue prominence may have been given to sodium and chloride in connection with the actions of both the adrenal cortex and the posterior lobe of the pituitary upon the excretion of water. While the thirst and polyuria of cats with experimental diabetes can only be modified by restriction of salt or water, Winter, Sattler & Ingram (97) found that they abated or vanished if such animals were deprived of all food, even if they had free access to water and were given moderate amounts of salt. The specific gravity of the urine, however, did not rise under these circumstances. This suggests that the fundamental disorder in diabetes insipidus is the inability to elaborate a concentrated urine. On the other hand Swann & Penner (107) found that the polyuria of rats with diabetes insipidus, though greatly aggravated by sodium chloride, Ringer's solution, or sodium carbonate, was not affected by sodium sulfate, sodium citrate, potassium chloride, or calcium chloride. Although Swann & Penner give no information about specific gravity in their experiments, Brull & Eichholtz (108) earlier reported that the specific gravity of the urine rose after potassium chloride and calcium chloride. Findley (109) has confirmed the observation of Lindeboom (110) that patients with diabetes insipidus, under the influence of mercurial diuretics, excrete large amounts of chloride in high concentration without increasing their output of water.

Heller (111), in an investigation of the distribution of the antidiuretic hormone of the posterior pituitary throughout the vertebrates, detected antidiuretic activity in pituitary extracts from mammals, birds, amphibians, and teleost and elasmobranch fishes. However, mammalian glands yielded far more than did glands from other classes of vertebrates. In frogs the injections of these materials had no antidiuretic action, but facilitated the



excretion of chlorides. Boyd & Whyte (112) also report that pitressin in frogs has no effect on the elimination of water, but promotes the excretion of chloride. Although pituitary extracts have no appreciable effect on the excretion of water or salts by fresh water fish, extracts from the glands of these species, according to Boyd & Dingwall (113), when injected into frogs, cause retention of water. Heller (114) claims that the antidiuretic principle of posterior pituitary extracts is distinct from the pressor principle. Whether there are two separate native hormones or not, he appears to have freed extracts of pressor activity without loss of antidiuretic potency by exposing them to heat at a pH of 10. In the frog, Boyd & Whyte (112) have found that pitocin causes retention of water, while according to Fraser (115), in the rat the oxytocic principle acts as a diuretic.

Experiments of Bayliss & Brown (116) and Haterius (117) support the view that the posterior pituitary does not control water excretion through the intermediation of the nerves to the kidney. It has been demonstrated repeatedly that, when given to animals which have been anesthetized by any one of a variety of drugs, posterior pituitary extracts are not antidiuretic, but may even provoke diuresis. Heller (114), because his purified antidiuretic principle, although it had no antidiuretic effect, did not induce diuresis in rabbits anesthetized with urethane, as unpurified extracts do, has concluded that the usual diuresis must be attributed to the pressor principle. The absence of antidiuretic effect he ascribes to the fact that anesthesia *per se* impairs the concentrating powers of the kidney. Bayliss & Brown (116) effectually denervated one kidney of the dog, by transplanting it, leaving the other *in situ*. Ether anesthesia had no effect on the function of the explanted kidney, although it inhibited in the normal kidney the polyuria that follows decerebration or hypophysectomy in animals with intact kidneys.

Evidence continues to accumulate that the activity of the posterior lobe of the pituitary is controlled by certain nuclei and tracts in the hypothalamus (117, 118, 119, 120).

Whether the actions of the posterior pituitary upon water and salt metabolism are directly antithetical to those of the adrenal cortex or not, Winter, Gross & Ingram (121) have shown that the concentrations of sodium and chloride in the serum do not fall so far after adrenalectomy in cats with diabetes insipidus as they do



in normal cats. Adrenalectomy also reduces the volume of the fluid exchange in cats with diabetes insipidus. Ingram & Winter (122) incline to believe that intake of fluid, not output of urine, is primarily affected. Britton & Corey (123) studied the water intake, urine volume, and chloride excretion of normal, adrenalectomized, and hypophysectomized rats without treatment and under the influence of either desoxycorticosterone or posterior lobe extracts. From these experiments it appears that desoxycorticosterone regularly promotes excretion of water in excess of chloride, while posterior lobe extracts further retention of water in excess of chloride. When both preparations were given to the hypophysectomized animals the action of the posterior pituitary predominated. In other respects the actions of the two glands appear to be quite unrelated, since the cats of Winter, Gross & Ingram (121) with polyuria did not survive adrenalectomy as long as did those with intact pituitaries, nor did the potassium in their sera rise more slowly.

#### THE ACTIONS OF THE ANTERIOR LOBE OF THE PITUITARY AND THE THYROID GLAND

Swann & Penner (107) found that totally hypophysectomized rats, in contrast to those in which the posterior lobe had been destroyed, but much anterior lobe substance left, did not develop polydipsia even when they were given salt solution to drink. Schweizer, Gaunt, Zinken & Nelson (124) in similar experiments measured, in addition to fluid intake, body weight, food intake, and urine volume. They agree with other observers that, after hypophysectomy, rats develop a self-terminative polydipsia which can be re-established by injections of anterior lobe extracts. They noted, however, that when the initial polyuria subsided the rats were taking almost no food, were losing weight, and were excreting quantities of urine which, though not unusually large for normal animals, were large in proportion to their water intake. Anterior pituitary extracts restored their appetites, causing them to take more food as well as water. Since starvation abolishes the polyuria and polydipsia of cats with diabetes insipidus (97) (*v. s.*) it may be necessary to determine how far the reputed diuretic effect of the anterior lobe derives from its ability to overcome cachexia. Schweizer *et al.* (124) were unable to restore polyuria and polydipsia in their rats by means of adrenal cortical extracts, from



which they infer that the diuretic action of the anterior lobe extracts does not depend upon the adrenotropic principle. White & Heinbecker (125) claim that acid extracts of the anterior lobe provoke diuresis in normal as well as in hypophysectomized dogs. This may also be connected with the metabolic disturbances which these extracts produce.

White & Heinbecker (125) have also confirmed the observation of Mahoney & Sheehan (126) that the polyuria produced in dogs by destruction of the stalk of the hypophysis is checked by removal of the thyroid, but can be restored by administration of active thyroid substance. The same authors, however, were unable to induce polyuria in dogs by means of dried thyroid after total removal of the hypophysis or of both the hypophysis and the thyroid. The combination of thyroid and anterior lobe extracts did have a diuretic effect on animals with both glands removed. In the rat White (127) could elicit no diuresis with anterior lobe extracts, even when thyroid was given at the same time. In cats with diabetes insipidus Ingram & Fisher (128) could detect no reduction of polyuria after thyroidectomy. The response of these animals to anterior lobe extracts was variable. Cutler (29) has reported some improvement in two patients with diabetes insipidus after thyroidectomy; but Findley (109) in another case could discern no effect from either thyroid extract or thyroidectomy. Paradoxically Jonáš (130) reports some improvement in three patients from administration of thyrotropic hormone.

#### THE ACTION OF SEX HORMONES

The discovery that steroids from the adrenal cortex, which have such striking effects on the metabolism of salt and water, are chemically related to certain of the sex hormones, has led to the investigation of the effects of the latter upon the same functions. Thorn & Emerson (131) observed a distinct fall in the sodium excretion of a castrate male after administration of testosterone propionate. This was, however, complicated by a simultaneous retention of nitrogen, potassium, and phosphorus. Moreover, no increases in the concentrations of sodium and chloride in the serum were demonstrated. On the basis of similar experiments in dogs Thorn, Nelson & Thorn (132) have claimed that estradiol, progesterone, estrone, pregnandiol, testosterone, and testosterone propionate all cause retention of sodium and water



in varying degrees. The data on which these claims are based are not presented in a form which permits analysis of their significance. Sharpey-Schafer & Schrire (133) could discover no changes in the urinary volume of fourteen human subjects which could be attributed to estradiol given in doses of 100,000 I. B. U. for from seven to ten days. The group included normal women before and after the menopause, castrate women, normal males, and one male with undeveloped gonads. All were maintained throughout the period of study, which included preliminary and after periods, on constant food and fluid intake. Thorn, Nelson & Thorn (132), from a study of fifty nurses and dietitians, each of whom was observed for thirty-five days so as to include a full menstrual cycle, have claimed that the menstrual cycle is characterized by rhythmical changes of weight which they ascribe to retention and excretion, respectively, of fluid and salt. The data defy analysis and are quite unconvincing. Neither diet nor fluid intake was controlled; nevertheless, significance is attached to changes of weight of the magnitude of one kilogram which seem to the reviewer to occur with no consistent relation to the menstrual cycle. Moreover the authors admit that approximately two thirds of those who gained weight during the menstrual cycle were aware that appetite as well as thirst increased at these times.

To draw an analogy between these equivocal weight changes and the striking retention of water that accompanies the counterpart of menstruation in old-world monkeys (134) is hazardous in the extreme, since these monkeys are provided with accessory organs, the so-called sexual skin, which the human does not possess. These undergo extraordinary tumefaction during the period of sexual activity. Clarke (135) has shown that this process is accompanied by thirst and oliguria, that the fluid retained has the characteristics of interstitial or extracellular fluid, that it is derived in part at the expense of the interstitial fluid of the body as a whole, and that it appears to contain protein.

#### ENDOCRINE CONTROL OF NORMAL WATER METABOLISM

Gilman & Goodman (136), in 1936, demonstrated that the urine of dehydrated rats contained material which resembled in certain respects the antidiuretic principle of the posterior lobe of the pituitary, and which, when injected into normal rats, had an antidiuretic action. This led them to suggest that the secretory



activity of the posterior pituitary was automatically regulated in conformity with the water content of the animal. Ingram, Ladd & Benbow (119) found antidiuretic activity in the urine of normal rats dehydrated by injections of hypertonic sodium chloride and purgation with magnesium sulfate, but could demonstrate none in the urine of cats with diabetes insipidus after similar treatment. Walker (137) also confirmed the observations of Gilman & Goodman on rats, although he found less antidiuretic activity than the latter did in the urine of dehydrated rats. Furthermore he found that the antidiuretic activity was preserved when the urine was rendered alkaline enough to destroy the antidiuretic activity of pituitrin and that it was restrained by cellophane membranes that were permeable to pituitrin. Urine from cats, even after total hypophysectomy, was slightly antidiuretic, regardless of their state of hydration. He was unable to detect pituitrin in the urine of rats after injection of the drug, in direct contradiction of the claims of Heller (138). Walker, however, employed methods of extraction and assay which were presumably more specific for pituitary antidiuretic principle than those which others have applied to urine. These experiments place the burden of more substantial proof upon those who would attribute to pituitrin the onus for all types of oliguria, including those that result from emotional stress and exercise (139), acetylcholine (140), nephrosis (141), and other physiological or pathological conditions. Walker (137) has pointed out that dehydration produces oliguria in the hypophysectomized, as it does in the intact animal, which could hardly be the case if the oliguria of dehydration were effected by pituitary secretion. It is notable that in most of these studies the excretion of water alone has been studied, with little or no effort to determine whether, in other respects, the oliguria has the earmarks of pituitary activity.

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DEPARTMENT OF INTERNAL MEDICINE  
YALE UNIVERSITY SCHOOL OF MEDICINE  
NEW HAVEN, CONNECTICUT



## GROWTH<sup>1</sup>

BY GEORGE S. AVERY, JR.

*Department of Botany, Connecticut College,  
New London, Connecticut*

In any satisfactory analysis of growth problems the morphological response of the organism should be critically studied in relation to both external and internal factors. At present, relatively few organisms are sufficiently well known to make this possible, thus perhaps the most fruitful experiments on the physiology of growth remain to be done. The literature on the subject continues to expand rapidly, however, and it is the object of this review to call attention to some of the suggestive or otherwise significant papers of the past two or three years, and to some extent to integrate them. Growth as here discussed includes the generally understood problem of organism increase in its broadest sense, and only a few special aspects of experimental control of differentiation are touched upon.

The slime molds are included here because they warrant the attention of all who are interested in problems of growth and differentiation. Only in this group of plants is the period of vegetative increase clearly separated from that of differentiation.

Since the growth and development of the organism is dependent upon the division, enlargement, and subsequent character of its cells, studies bearing on intracellular as well as intercellular relationships have a basic significance.

### CERTAIN CELLULAR ASPECTS OF GROWTH

The relationship between nuclear and cell volume (cytonuclear ratios) in root and stem tips of numerous higher plants, and also in *Elodea* leaves and stem hairs of tomato, has been reported on by Trombetta (1). In general, even in cells in the same stage of development, the nuclear volume increased less rapidly than the cell volume although the cells were sometimes of different sizes; thus the actual cytonuclear ratio changed considerably; the rates of change in the size of the two structures were found constant, however. From a review of the literature on nuclear and cell size in relation to growth, Trombetta (2), concludes that they are not

<sup>1</sup> The papers reviewed here deal only with growth and differentiation in seed plants and slime molds.



regulating factors in cell division; thus the relationship is probably not as important a factor in growth as many earlier workers regarded it.

In a study on cell and nuclear size in inbred and hybrid tomatoes, Whaley (3) reports decreasing cell and nuclear size in terminal meristems . . . as the plant grows older; this decrease is less rapid in the hybrids than in the pure types.

From studies on the roots of certain small-seeded grasses, Sinnott & Bloch (4) report that changes in intercellular relationships result from different rates of growth in different parts of the cell wall. They found no evidence in *Poa*, *Phleum*, etc., for "sliding growth," since transverse walls in adjacent longitudinal rows do not approach or pass each other; surface forces and differential cell division are also regarded as not significant in cellular readjustment in the roots studied. Thus the problem of cellular adjustment in growing tissues of certain organisms comes down to differing rates of growth in different parts of the cell wall. The position of newly formed walls in relation to those already present has been reported on also (5).

The importance of the growing point, or terminal meristem of higher plants, lies in the fact that it is essentially the functional embryo of the plant. It remains undifferentiated, gives rise to new cells continuously, and is the ultimate source of all normally produced organs once the plant is beyond the initial embryonic stage. Whaley (3), reporting on terminal growing points of stems of hybrid and inbred tomatoes, finds no relation between volume of growing point and heterosis; the size of the growing point is more closely related to the size of the leaves, etc., developed from it. Bindloss (6), in a cellular analysis of tallness and dwarfness in tomatoes and zinnias, finds from cell studies on the terminal growing region that cell division is more rapid in tall plants, and that their tallness therefore is due to a greater number of cell generations. The difference in height between genetically tall and dwarf varieties was not attributable to differences in meristem size nor to cell size within the meristem. The review by Foster (7) of cellular organization at the growing points of seed plants makes repetition unnecessary here, but the need is apparent for experimental studies rather than descriptive studies.

In a study of the conditions of formation and subsequent growth of dwarf embryos of rye, Nutman (8) concludes that the



relationship between embryo size and subsequent growth rate is contrary to that postulated by Ashby in connection with hybrid vigor. Ashby's observations on maize embryos, etc., led him to the conclusion that hybrid plants were larger as a result of starting from larger embryos.

The most important recent experimental study on growing points of higher plants is that of Satina, Blakeslee & Avery (9), who report the production of periclinal chimeras in *Datura* as a result of colchicine treatment of seeds. By means of these experimentally induced chimeras it has been possible to demonstrate the presence of three independent cell layers ("germ layers") in the stem tip of *Datura*. Various combinations of  $2n$ ,  $4n$ , and  $8n$  components gave nine types of periclinal chimeras in which one, two, or three cell layers were polyploid in varying combinations. The chief significance of the work is the demonstration that in *Datura* the different cell layers at the growing point (i.e., primary meristems) retain their individuality, and tissues coming from them can be readily distinguished.

Brain (10), in a study of the cellular effects of prolonged rotation of plants on a horizontal clinostat, reports changes in cell shape and size in the flower stalk, etc., of *Narcissus*, and also in the smaller epidermal and palisade cells in the leaves. Other species reacted differently but gave characteristic cellular changes.

#### MORPHOGENETIC ASPECTS OF GROWTH OF PLANT ORGANS

Cell-organ morphogenetic relations have been studied by Sinnott (11) in different stages in the development of the fruits of twelve races of *Cucurbita pepo*. It was shown that in each tissue of the fruit, growth is at first characterized chiefly by cell multiplication, although cell size increases slowly also. After a specific cell size is reached, division ceases and all further growth is by cell enlargement. From the innermost tissues outward, successively outer ones show more rapid increase in size during the cell division period, earlier cessation of division, and therefore larger cell size when division stops.

Houghtaling (12), in a study of stem morphogenesis in three varieties of tomato, finds that differences in stem size are accompanied by differences in cell number in the pith and cortex, whereas cell size appears to be a function of age. As for growth rates of the various tissues in relation to the stem as a whole (transectional



studies): cortex grows more slowly than the stem, vascular cylinder more rapidly than the stem, while pith grows at the same rate as the stem.

The region of most rapid elongation in the hypocotyl of the *Brassica* seedling migrates upward from the base to the cotyledonary node (13). Cell division occurs in the underlying tissues throughout the hypocotyl, but persists longest near the node. Epidermal cells do not increase in number appreciably during hypocotyl elongation. Several drastic treatments failed to change the growth characteristics described.

#### ANALYSIS OF GROWTH

Pratt (14) discusses the validity of equations for relative growth constants when applied to sigmoid growth curves, and states that logarithmic plotting of growth data in accordance with Huxley's formula is not a satisfactory substitute for the original data plotted as time curves. Pratt points out that when the total growth periods are unequal or when they are equal but do not coincide in time, a straight line cannot accurately fit all of the points, although isolated portions of the growth cycles may yield curves that are approximately linear over relatively wide ranges. Thus a sharp break in the relative-growth curves does not necessarily mean a fundamental physiological change in the organism, but may be merely the consequence of comparing two quantities whose periods of increment are not entirely concurrent. He concludes that although Huxley's equation often reveals interesting relations among differentially growing quantities, its use is restricted by definite limitations.

#### EXTERNAL FACTORS REGULATING GROWTH

*Light.*—White (15) reports that root length in *Lemna* is directly related to light intensity in the range of 50 to 300 foot candles (continuous illumination). Reduction of light intensity leads to decrease in root length; thus in *Lemna* root growth and photosynthesis appear to be intimately related.

That photoperiod and light intensity may influence flower structure has been shown in tomatoes by Howlett (16), who obtained maximum pistil length in relation to stamens when the plants were grown under a short photoperiod and light of low intensity (with an adequate supply of nitrogen). Higher light intensity shortened the pistils somewhat, and a long photoperiod at high intensity had the greatest relative pistil-shortening effect.



Popp & Charlton (17) in studies on the influence of ultraviolet radiation upon the germination and seedling development of several species of plants, report that the most notable effect of ultraviolet radiation is to reduce the stature of the plants; this effect increased with decreased wave length, with increased length of exposure, and with increased intensity of radiation. There were no stimulative effects, either on germination of seeds or elongation of seedlings.

Withrow (18), in a study of the responses of pea, maize, soybean, potato, tomato, and cocklebur seedlings to low intensity radiation, reports that plants growing under the longer wave lengths of the visible spectrum, as contrasted with dark-conditioned plants, have larger leaves and shorter hypocotyls and first internodes. Dry weights of the hypocotyls and first internodes were reduced, whereas those of the root and first leaves were greater than those of dark-grown plants. Light of the longer wave lengths increased the total amount of reserves translocated from the cotyledons. The accelerated transport was greater toward the stem apices than to roots.

Went (19) has repeated the work of earlier investigators, showing that leaf size of seedlings grown in darkness can be increased by exposure to minute amounts of light. He reports that short exposures of low energy value in the blue, yellow, and red portions of the spectrum are effective in increasing leaf size in pea seedlings, whereas equal energy in the green is ineffective. As regards seedling stem growth, Went notes that it is independent of any light reactions, since most rapid growth occurs in complete darkness, and is inhibited by light; most pronounced inhibition in pea seedlings was reported for the red and yellow portions of the spectrum.

Length growth of excised roots of *Datura* cultured *in vitro* was inhibited by exposure to the diffuse light of the laboratory (20), and thickening of the roots occurred in the growth-inhibited regions. In the thickened portions clusters of long root hairs often appeared. Elongation occurred at night, so that in such roots tufts of root hairs appeared at intervals along the roots. This corroborates the early work of Deveaux (*circa* 1880).

The inhibitory effect of light upon the polarized growth of the first internode of the *Avena* seedling has been studied by Goodwin (21), who reports two distinct phases in the inhibition of elongation. The first is characterized by high sensitivity to radiant energy: effective wave lengths extend from the long ultraviolet to



infrared, visible red being most effective. The result of a five-minute exposure, with total radiant energy of 81 ergs per sq. mm., was inhibition of cell division. The second phase of inhibition is characterized by a much lower sensitivity to radiant energy, and the result is to inhibit cell elongation. Wave lengths in the visible spectrum, and on up to 16,000 Å, are effective in inhibiting cell elongation, whereas wave lengths longer than this still affect cell division. Goodwin further observes that the radiant energy causing the inhibition may be received by any part of the seedling shoot. Schneider (22), in a study of the elongation of excised segments of the first internodes of *Avena* grown in culture solution, reports that light has an inhibitory effect upon elongation.

McIlvaine & Popp (23), studied the growth hormone content of seedlings in relation to light and growth. They reported on *Brassica* seedlings grown for 3½ and 7 days, and irradiated periodically under various conditions with daylight, Mazda, and mercury vapor lamps. Hormone content (*Avena* test) of shoot growing points was directly related to growth, i.e., seedlings grown under short wave lengths of light were shorter, and their hormone content was also lower; growth hormone is evidently inactivated by daylight, and tends to accumulate in darkness.

*X-rays*.—Naylor (24) exposed mature *Bryophyllum* leaves to x-rays for periods of one to eighty-five minutes. At the energy level studied, five-minute exposures retarded growth of the foliar embryos, and thirty-minute exposures had a marked inhibiting effect. There was no evidence of injury in the X-rayed leaves.

Johnson (25) x-rayed wheat seeds with 1,000 to 60,000 r. Plants from seeds soaked before irradiation with 5,000 r or more died within three weeks; dry seeds given the same irradiation were reported as exceeding the controls in tillering, height, and weight. Seedlings from soaked grains exceeded controls only in tillering. Wort (26) irradiated seeds of Marquis wheat with filtered x-rays of 19 to 228 r. The most rapid growth rate was produced by 114 r, irrespective of seed age. Greatest fresh and dry weights of plants grown from five-year-old seed resulted from treatment of the seed with 76 r, whereas one-year-old seeds gave plants with the greatest dry weights when irradiated with 57 r. Irradiation with 76 to 114 r accelerated heading and flowering of plants grown from old seed, but retarded that of plants grown from one-year-old seed. In Fulhio winter wheat, Wort reports that seedling height and weight



increased with all doses of x-rays used, the best response being obtained with 114 r.

In contrast to the foregoing, many studies not reported here show no growth-accelerating or otherwise beneficial effects from x-radiation. It should be pointed out, perhaps, that almost any type of organismal response might reasonably be expected from x-raying. Inherent alterations in growth rate or growth habit only reflect modifications in genetic constitution, and there is little reason to suppose that any two workers might succeed in inducing the same changes.

*Electric potentials.*—Watanabe *et al.* (27) observed an increased potential difference between the front and rear portions of myxomycete plasmodium as a result of applying indoleacetic acid to the front. A concentration of 156  $\mu\text{g. per l.}$  was more stimulating than higher concentrations, and 20 mg. per l. depressed the potential difference. The threshold concentration for potential difference stimulation was about 39  $\mu\text{g. per l.}$  Dinitrophenol, *l*-histidine, or urea in appropriate concentrations also affected the potential gradient. It is suggested that the indoleacetic acid effect on potential difference is due to activation of the oxidative metabolism.

*Gases.*—For tomato plants growing in liquid culture, it has been shown that stem and leaf production, within certain limits, is proportional to the rate of aeration of the nutrient solution; greatest production was obtained with 250 cc. of air per plant per min. (28). Optimal fruit and root production, on the other hand, was obtained with as little as 2.5 cc. of air per plant per min. Laing (29) reports that the shoots of most water plants studied grow best in a medium low in oxygen, and that roots grow best when the oxygen content is high. The effects of unsaturated hydrocarbons and of auxins in gaseous form are discussed by Zimmerman, Hitchcock & Wilcoxon [(30), and in later papers].

*Temperature.*—Elongation of the stems of field-grown asparagus has been reported on by Culpepper & Moon (31). For temperatures between about 52° and 87°F. the relationship between temperature and growth rate is almost linear. The rate of stem elongation is reported to be greatest in the region a short distance below the tip, in common with the vast majority of higher plants.

Brown (32) has described equipment for growing plants under conditions of controlled soil and air temperatures, each being controlled independently of the other.



Lindner (33), in a study of the factors that affect regeneration of small isolated segments of the horse-radish root, concluded that buds are more affected than roots by temperature changes. Between 15° and 25°C. the  $Q_{10}$  for bud initiation was 2.8, that for root initiation 1.6. The optimum temperature for root and bud initiation was 26°C.

Literature bearing on the effect of low temperatures, etc., in hastening the reproductive period in certain plants (vernalization) has recently been reviewed by McKinney (34).

*Atmospheric pressure.*—No very recent work has appeared in this particular connection, aside from that of Pease (35) who reports that hydrostatic pressures applied to portions of slime mold plasmodium first reduce the viscosity of the plasmasol and the rigidity of the plasmagel so that surface tension plays an important role in the form changes and streaming. Pressures of 4,000 lbs. per sq. in. or more induce unidirectional streaming.

The work of Dutt & Guha-Thakurta (36) is worthy of mention: at reduced atmospheric pressures of 360 mm. Hg, seedlings of *Cajanus* showed diminished growth; *Helianthus* seedlings were unaffected. At a pressure of 260 mm. Hg, growth ceased in the former plant and decreased in the latter. Cessation of growth occurred at 360 mm. Hg in the primary root of *Cicer*. However, when the partial pressure of oxygen was maintained equal to that in the atmosphere, growth was unaffected at the pressures studied.

*Water pressure.*—Funke & Bartels (37) report that the petioles of a large number of water plants elongate rapidly; petioles of *Limnanthemum nymphaeoides* may elongate from 30 to 100 cm. in forty-eight hours. Petioles of female flowers of *Vallisneria spiralis* may elongate as rapidly as 2 cm. per hr. for an entire day. Such growth is attributed to both cell division and cell elongation. Synthetic growth substances such as naphthaleneacetic, indoleacetic, and indolebutyric acids seldom cause any more rapid growth, but commonly bring about twisting of the petioles. *Nuphar advenum* is reported as growing best under water pressures not exceeding 4 to 6 feet, but pressures as great as 9½ feet did not prevent growth (29).

*Wound response.*—The effect of wounding on root formation in *Coleus*, tomato, and a number of other species, has been reported on by LaRue (38). He finds in most instances that wounded cuttings produced two to three times as many roots as the controls. Naylor (39) reports that injuries to the roots and stems of young dill plants, during transplanting, result in a strong tendency to



flower, and that such wound-induced flowering may obscure the results of photoperiod experiments. Other aspects of plant wound responses are reviewed extensively by Bloch (40).

*Mineral nutrition, radioactive isotopes.*—From a study on the relation of nitrogen supply to the growth of inbred and hybrid maize, Burkholder & McVeigh (41) report that all hybrids exceeded either one or both parental lines in dry matter produced under conditions of high nitrogen nutrition, though some lines were little if any better than the more vigorous parents; they thus correlated more striking cases of heterosis with capacity to utilize supplied nitrogen. Stem size increased directly in proportion to nitrogen supply, as did both size and number of constituent parenchyma cells; the size of xylem and phloem cells also was directly proportional to the nitrogen supply.

Richards (42) reports that at very low potassium levels barley seedlings cease growth at the first or second leaf stage, but that upon addition of rubidium to the solution, growth proceeds normally. Rubidium in excess induces short thick roots and early leaves which are wide, dark green, waxy, brittle, twisted, and which have prominent midribs.

Reed & Beck (43) have shown the importance of zinc in the growth of maize, as determined by height, dry weight, etc. Shortened internodes and banded chlorosis of the leaves were characteristic of zinc-deficient plants, as was also curtailed production of cobs and kernels. Although the equations for the growth curves were similar for plants receiving zinc and for those not receiving it, the values of certain constants were greater in the case of the plus-zinc series.

Terminal buds and stem segments of zinc-deficient tomato and sunflower plants yielded only small amounts of auxin or none at all ("diffusion" method), and the decrease in auxin preceded the appearance of visible symptoms of zinc deficiency (44). In copper- and manganese-deficient plants, auxin decreased only after symptoms of deficiency had developed. Retardation in stem elongation in all three types of deficiency roughly paralleled the decrease in auxin. The author concludes that zinc is important for the maintenance of auxin in the active state, but is not required for its synthesis by the plant.

From experiments on the transport of radioactive sodium, phosphorus, and bromine ions in *Avena* coleoptiles and *Helianthus* hypocotyls, it is reported (45) that these ions move both apically



and basipetally, whereas indoleacetic acid moves exclusively in a basipetal direction.

Arnon, Stout & Sipos (46) present a discussion of methods with radioactive isotopes, and report that forty minutes after supplying radioactive phosphorus to tomato plants six feet in height, it could be detected throughout the plant. They also have described a technique for making contact radiographs to show the distribution of newly absorbed phosphorus in plant tissues.

Vickery *et al.* (47) supplied isotopic ammonium ions in the culture solution to the roots of tobacco and buckwheat plants, and found that it was rapidly absorbed and transported to tissues in all parts of the plant; within a short time the isotope was detected in the amide groups of asparagine and glutamine, and in the fraction which included free amino acids. Appreciable amounts also were found in the proteins of roots, stems, and leaves, but from the concentration of isotopic nitrogen the greatest intensity of assimilation appeared to be in the roots, least in the leaves.

Biddulph (48) injected radioactive phosphorus into bean leaves and found that its migration and distribution vary throughout the day, the initial migration being predominantly downward. During the evening hours 40 per cent of the migratory phosphorus reached the root system, but the greatest total downward migration took place about 10 a.m. and the least at approximately 10 p.m.

*Growth factor "nutrition" of tissue and organ cultures.*—A recent review of the subject (49) covers significant work through most of the year 1939. Addicott & Devirian (50) report that for successful culture of pea roots *in vitro*, nicotinic acid as well as thiamin must be added to the usual culture solution. Of twenty-three substances closely related to nicotinic acid, Bonner (51) reports that only nicotinamide, and esters of nicotinic and nicotinuric acid are adequate in the nutrition of excised pea roots. Tauja-Thielman & Pelece (52), studied the effect of 3-indoleacetic acid on excised roots growing in culture, and found that the addition of the growth substance is most beneficial in cases where growth is normally poor, and is least effective where good growth is normally obtained. Concentrations toxic to tomato roots are growth promoting for maize roots.

Excised roots of an  $F_1$  heterotic tomato plant grow more rapidly and produce more dry matter than those of either parent, reports Robbins (53), when the culture solution contains thiamin, pyridoxin ( $B_6$ ), and nicotinamide . . . or any one of the four substances.



In one passage, however, addition of thiazole to the culture solution led roots of one of the inbred parents to exceed the growth of the  $F_1$ .

From studies *in vitro* on the culture of embryos of *Datura*, van Overbeek, Conklin & Blakeslee (54) report that embryos isolated from seeds when 2 mm. in length (about one third final size) can be grown to maturity in culture, in a basic medium containing a mixture of vitamins, etc. Proembryos could not be grown in this medium. The addition of nonautoclaved coconut milk to the basic medium made it possible to culture the very young proembryos and grow them to maturity, thus establishing coconut milk as a source of unknown growth factors which are capable of stimulating the normal growth of immature embryos *in vitro*, and also pointing the way to a test method for the detection of such factors.

Potentially unlimited growth *in vitro* of hybrid *Nicotiana* callus tissue (in fully known nutrients) has been reported by White (55), such cultures having been maintained through forty week-long passages. Cultures increased about three-fold in volume each week. Histological study indicates that except for occasional scalariform cells, the cultured tissue shows no evidence of differentiation or polarity—thus a true plant tissue culture.

For growth of gall tissue in culture, and its capacity to continue to grow as tumor tissue when grafted into normal tissue, see p. 133.

*External application of growth substances and normal growth.*—This subject has been reviewed recently [(57), pp. 63–66], and references to earlier work may be found there. Generally speaking, the application of physiologically active substances to plants affects differentiation rather than growth. However, Mitchell & Stewart (58) report that naphthalene acetamide applied to bean plants in strong concentrations, in an emulsion spray, inhibits terminal bud and primary leaf development but stimulates root growth; lower concentrations of the spray accelerate top growth somewhat. Mitchell (59) has shown, further, that naphthalene acetamide promotes cambial activity.

Gouwentak & Maas (60) have provided the first experimental proof that the cambial stimulus resulting from the application of auxin in a woody plant, *Fraxinus ornus*, can be transmitted for an appreciable distance down the stem. However, if auxin activation of the cambium is to occur, it is necessary to apply auxin at just the right time in the spring of the year when the cambium is "auxin sensitive." Applications of 100  $\mu$ g. of indoleacetic acid in



lanolin to the decapitated twigs led to cambial activity in the entire length of the twigs (12 to 23 cm.).

Söding (61) has shown that indoleacetic acid applied to decapitated stem tips of *Helianthus* in a concentration of 200 $\mu$ g. per l. (each plant receiving  $1.35 \times 10^{-4}$   $\mu$ g. per hr.) would activate the cambium, but that indoleacetic acid is not the only substance which will experimentally activate cambium. Scrapings from *Acer* cambium when applied in agar to *Helianthus* gave the best stimulation, and led Söding to conclude that "co-auxins" are essential for good cambial activation. Mullison (62) reports cambial activity somewhat stimulated in stems of young decapitated bean plants as a result of applying tetrahydrofurfuryl butyrate to the decapitated stump.

There have been many studies on the role of auxin in correlative inhibition, i.e., the inhibition of growth of certain portions of plants while growth goes on in other portions (such as the growth of the terminal bud and the accompanying suppression of growth of lateral buds). Among these are the works of Went (63), Skoog (64), and Gustafson (65).

Maize seedlings when exposed to vapors of auxins (in light or darkness) gave marked growth responses: etiolated coleoptiles and first internodes underwent excessive elongation (30).

Barton (66, 67) has studied the effect of treating numerous varieties of nondormant garden seeds with potassium  $\alpha$ -naphthalene acetate and indolebutyric acid, applying them as vapors, liquids, and dusts. In no case was there an increase in percentage germination, nor in speed of germination; injury was obtained at higher concentrations. Increased length of seedlings from treated seeds was reported for nine of the twenty-five varieties treated, but the growth stimulation came only in filter paper cultures—never in soil cultures. Observations on rate of maturity revealed no stimulative effects as a result of treatment. The only marked morphological effect was on the shape of radishes treated with high concentrations. In her second paper Miss Barton reports chiefly on the effect of soaking seeds of two species of dogwood (*Cornus*), crab apple, and domestic apple, in synthetic growth hormone solutions. These seeds ordinarily fail to germinate without pretreatment at low temperatures, and hormone pretreatment had no stimulating effect. Seeds of the American elm (*Ulmus americana*) which do not require low temperature pretreatment for germination, showed improved germination after treatment with hormone.



Landau (68) reports that in preliminary experiments certain concentrations of indoleacetic acid stimulated the germination of oats, French beans, etc., whereas other concentrations were inhibitory; the inadequacy of the controls was mentioned by the author.

#### EXTERNAL FACTORS REGULATING DIFFERENTIATION

*Photoperiodism.*<sup>2</sup>—Relatively few effects of physical factors on differentiation in plants are well understood, but one of the problems now being investigated intensively in several laboratories is that of the influence of fixed-length periods of light and darkness on floral initiation. The more important current experimental studies in this field of "photoperiodism" are on factors influencing the behavior of growing points of higher plants, i.e., the transition of the growing point from a state of vegetative activity to one of flower production. The problem is clearly one of control of organ differentiation, and as such merits the attention of physiologists.

In studies on photoperiodism the only method of determining whether flower primordia have been initiated is direct observation, i.e., the appearance of flower buds. More critical workers of the past few years have resorted to dissection methods which make it possible to discern the presence of flower primordia soon after the treatments are given (69). A relatively recent advance, confirming the earlier work of Cajlachjan and of Moskov, is the determination that the locus of photoperiodic perception is the leaf (70); Borthwick & Parker (71) have demonstrated that the capacities of different leaves to supply a flower-forming stimulus in response to environmental changes is correlated with their state of maturity. The most effective leaf in this capacity is the one which has most recently attained its full size.

Harder & von Witsch (72) report that *Kalanchoe blossfeldiana* is a short-day plant while young, and becomes increasingly indifferent to day length with increasing age.

A further attack has been made on factors affecting floral differentiation by attempts to evaluate the relative importance of the dark and light phases in photoinductive cycles that result in floral initiation. In earlier work on Biloxi soybeans (70) it was found that

<sup>2</sup> It is a pleasure to express my appreciation to H. A. Borthwick and M. W. Parker for generous help in evaluating the literature in this field, also for their criticism of the manuscript. Thanks are likewise due R. B. Withrow for criticism of the manuscript.



flower primordia differentiate in response to two or more short photoperiods, provided the intensity is of the order of 100 foot candles or higher. However, a much more vigorous response occurs if the intensity is greater than 100 foot candles. This intensity relationship suggests a correlation with photosynthesis, and indeed it has been shown (73) that floral initiation can be entirely suppressed or greatly reduced either by withholding carbon dioxide or by supplying light of intensity less than 100 foot candles. The importance of light intensity has been further pointed out by Naylor (39) and others.

It has been shown by various workers that dark periods have a controlling influence on floral initiation in short-day plants, and from this it might be inferred that dark periods are an essential part of photoperiodic phenomena. For example, *Xanthium*, a short-day plant, is reported by Hamner & Bonner (74) to respond to one long dark period, if grown under ideal conditions for induction, and Hamner (75) reporting on various cycles of light and darkness in relation to flower differentiation in Biloxi soybeans, *Xanthium*, etc., presents evidence which suggests that photoperiodic induction is dependent in part upon responses which occur as a result of exposure to light (A), and in part upon responses which result from exposure to darkness (B). The resultant changes (C) lead to floral initiation. (It is possible that the suggestion of the sequence A, B, to C may aid analyses of the problem in certain species.) However, Borthwick & Parker (76) have shown that several varieties of soybeans will initiate flower primordia even though grown continuously in light, thus showing that reactions leading to floral differentiation are able to proceed during the light period. In the case of some varieties these reactions may proceed at such a rate in continuous light that flower buds are actually formed, while in others the rates may fall short of this to varying degrees, in which cases no flower buds are formed. In both types, however, floral initiation occurs more rapidly if dark periods are included in the treatment, and in some varieties floral initiation seems to occur only if dark periods are included. (Continuous irradiation, but with part of the cycle at low energy levels, also induces flowering.) These results may be interpreted as meaning that flower-differentiating reactions in short-day plants can occur in both light and dark but that they proceed more rapidly in the dark (or at low levels of radiant energy). In long-day plants, such as aster, spinach, *Rudbeckia*, and dill, and in indifferent plants such as tomato, flowering can be in-



duced under continuous high radiant energy; a dark period is not required.

In studies on the effect of supplementary radiation of various wave bands on the photoperiodic response of certain plants, Withrow & Withrow (77) grew several different kinds of long- and short-day plants under short winter days, and days lengthened to twenty-four hours by blue, yellow-green, and red radiation. The longer wave lengths of the visible spectrum are primarily effective in producing the flowering and vegetative effects secured under long-day treatments with both the long- and short-day plants used; thus the initial photochemical step appears to be similar for all the plants tested.

Temperature also has a marked effect upon the photoperiodic process (39, 78). Exposure of the entire soybean plant to low temperatures inhibits floral initiation, but such experiments do not indicate what process or processes are inhibited (79). Studies on the transport of the flower-differentiating stimulus from the leaf to the growing point show that cooling the leaf petioles to 3°C. greatly suppresses the translocation of the stimulus (80). Initiation of flower buds is also greatly suppressed when the growing points themselves are cooled to 3°C., even though abundant flower-differentiating stimulus is being supplied by the leaves.

The fact that *Xanthium* responds to one long dark period, whereas the soybean requires at least two, would suggest that photoperiods may not be all-important in floral differentiation; and indeed, the work of Long (81), Roberts & Struckmeyer (82), Mann (83), Snyder (84), and others shows that environmental conditions of light and temperature either before or after the photoinductive cycle can influence the effect of a single long dark period.

The influence of wounding on flower differentiation (39) has already been referred to under "Wound Response."

Melchers (85, 86), from grafting studies with *Hyoscyamus* and *Nicotiana*, originally postulated the existence of two substances of a hormone nature to explain his results on flowering, but in his latest paper (87) he reports being unable to confirm the existence of such hormones.

The Russian work, particularly as it relates to hormones as possible agents which transmit the flower-differentiating stimulus from leaf to growing point, has been ably reviewed by Cholodny (88).

That photoperiodic phenomena are not causal in floral organ



(as opposed to vegetative) differentiation alone is clear from the work of Hamner & Long (89); they report from studies on tuber formation in *Helianthus tuberosus* growing under long and short photoperiods that changes occur in the leaves which lead to tuber formation. Even one leaf of a plant on a short photoperiod was sufficient to induce tuberization.

*Nitrogen and tissue differentiation.*—Burkholder & McVeigh (41) report that xylem and phloem differentiation was inhibited in maize plants grown on a low nitrogen supply, whereas in plants of the same genetic constitution but with ample nitrogen, these tissues developed in a characteristic manner. Only when the nitrogen supply was adequate did the phloem tissue possess typical sieve tubes and companion cells; and similarly, only with adequate nitrogen supply did the xylem form with large, normal, spiral, and pitted vessels.

*Auxins and leaf form.*—Zimmerman & Hitchcock (90) report that  $\beta$ -naphthoxyacetic acid when sprayed on leaves of tomato and other plants in concentrations of from 0.1 to 1 gm. per l. brings about modifications in size, shape and type of leaf, number of leaflets, etc.

*Auxins and parthenocarpic fruits.*— $\beta$ -Naphthoxyacetic acid is also reported to be (90) capable of producing seedless fruits in tomato, if sprayed on the flower buds just as they are beginning to open (in concentrations of 0.4 to 0.5 mg. per l.). Wong (91) has produced seedless fruits in watermelon and other *Cucurbita* species by applying naphthaleneacetic acid and other growth substances (in lanolin), both alone and in combination, to the stigma or cut surface of the style of the unpollinated flower. Gardner & Marth (92) have tested the effectiveness of several different growth substances for their capacity to stimulate the production of seedless fruits in holly, and Yasuda (93), Gustafson (94), and others have continued their earlier studies in this field. Janes (95) in a study of the chemical differences between artificially produced seedless fruits of tomato, and normally pollinated ones, reports marked differences in titrable acidity, starch, and sugar content.

#### INTERNAL FACTORS REGULATING GROWTH: NATURAL AUXINS

*Occurrence and extraction.*—Zhdanova (96) from a brief study of *Vicia*, *Hydrangea*, *Chrysanthemum*, *Nicotiana*, etc., concludes that auxins are produced in growing points of plants at the expense



of sugars produced during photosynthesis in the leaves. Van Overbeek (97) reports that auxin is produced in isolated roots of *Pisum* cultured *in vitro* under sterile conditions. Shafer (98) points out that the prostrate habit of "lazy" corn is associated with abnormal distribution of auxin in the plant.

Other papers of a similar nature might be mentioned here, but it is clear from numerous studies that methods must be considerably improved before it will be possible to make critical studies of the relationship between auxin distribution in the organism and normal growth. The present steps being taken in this direction involve improved extraction techniques (99, 100, 101). It is already clear that no one method is satisfactorily applicable to all tissues, but Avery, Berger & Shalucha have described the first method for total and immediate extraction of auxin and auxin precursor from a plant tissue.

Stewart (102) reports an ether-extractable growth-inhibiting substance in cotyledons of radish seedlings; it hydrolyzes readily to form an auxin. This and other work on inhibitors points the way to an understanding that many substances, growth-inhibiting as well as growth-promoting, are concerned in normal growth regulation.

Other types of hormones than auxin are reported for higher plants, e.g., the so-called wound hormone (traumatic acid) which together with some of its analogues (103) is active in the unstandardized bean test, and the substances which favor the growth of leaf blades, such as adenine, etc. (104, 105).

*The physiological roles of auxin.*—Although diverse growth effects may be brought about through the application of indoleacetic acid and other auxins to living tissues, the fundamental role of such substances remains to be demonstrated. The problem has been approached by Sweeney & Thimann (106), who report an increase in the rate of protoplasmic streaming in the *Avena* coleoptile upon addition of 0.01 mg. per l. of indoleacetic acid (and 1 per cent fructose); and also by Commoner & Thimann (107), who report that the four-carbon acids provide a respiratory system which is part of the chain of growth processes, and that this is in some way catalyzed by auxin. However, the respiration affected is shown to represent only about 10 per cent of the total; thus to date, relatively unimportant respiratory increases have been experimentally produced as a result of supplying auxin. Albaum & Commoner



(108) present further evidence to show that the system of four-carbon acids is of importance in the control of plant growth by auxin.

Avery & Linderstrøm-Lang (109) report a correlation between high peptidase activity and high natural auxin content at the tip of the *Avena* coleoptile. It has been shown by Mitchell, Kraus & Whitehead (110) that applications of naphthalene acetic acid directly or indirectly increase the rate of starch digestion in bean leaves, and Mitchell & Whitehead (111) report that several different auxins, if sprayed on normal bean leaves (at 74°-76°F.), will bring about a marked increase in the rate of starch digestion; however, phenylacetic acid and naphthalene acetamide have no effect.

Mitchell & Stewart (58), Kraus & Mitchell (112), and others have shown that the application of certain synthetic auxins to young bean plants induces mobilization of solid materials at the place of application.

Diehl *et al.* (113) from certain experimental and theoretical considerations conclude that the primary effect of growth hormone is on cell walls, a view set forth earlier by others. From the assumption that auxin in a low concentration increases the swelling power of the intermicellar material, and that in a higher concentration it weakens here and there the connection places of the fringes in the network of cellulose micelles, and that in still higher concentrations it weakens many of these junctions, they conclude that it is easily understandable that parenchyma cells under normal conditions grow especially in length; also that under the influence of higher concentrations of growth hormone such cells grow more in width. This is an interesting approach to the mechanics of polarized growth, and deserves further study.

Skoog *et al.* (114) studied the effects of auxin on exudation, and report that in *Pisum* seedlings, auxin increases both rate and duration of exudation; in *Helianthus* plants the stimulating effect of auxin is mainly on the rate of exudation.

*Abnormal growth and galls.*—The earlier work of Kraus and associates (cf. 57) shows that 3-indoleacetic acid and several other physiologically active substances produce galls when applied to young decapitated stems of certain plants in relatively high concentrations; Mitchell (59) also observed gall production in beans thus treated with naphthalene acetic acid. Mullison (115), Kraus (116), and Blum (117) have further shown that tumor formation occurs as a result of applying auxins and other substances to de-



capitated young stems of bean and sunflower. In relating this and other work on experimentally induced galls to those produced by crown-gall bacteria, Riker, Henry & Duggar (118) observe that evidence is lacking for the view that indoleacetic acid, or any similar growth substance produced by crown-gall bacteria, plays a major role in pathogenicity; indeed, by the auxin extraction method employed, they report no significant difference in the auxin content of tomato stems grown at 27°C. (where galls develop) and at 31°C. (where galls do not develop). Levine (119) has produced crown-gall-like tumors in *Kalanchoe* by applying scharlach red (1 per cent in ether) to decapitated very young stems. Other animal carcinogens produced only necrosis of the treated zone.

Although gall formation is not prevented by the use of colchicine, Brown (120) reports that brushing the surfaces of bacterial tumors with this substance is an effective method for inhibiting further growth, and eventually kills the tumor. Of 305 tumors thus treated, 239 died though other parts of the plant remained healthy; 49 tomato tumors included in this total failed to succumb to the treatment. Similar treatment of tumors induced by indoleacetic acid inhibited their further growth, but did not kill the tumors.

White & Braun (56) have established what appears in every way to be a true plant tumor. They report that bacteria-free secondary tumor tissue from young sunflower stems, originally produced through the action of the crown-gall organism (*Phylomonas tumefaciens*), can be cultured *in vitro* free from the causal organism, and that upon grafting back into healthy sunflower plants it will grow typical crown-gall tumors. These induced tumors have a histological structure considerably more uniform than that of most crown-galls, with extensive hyperplasia but relatively little disorganization.

#### GROWTH AND DIFFERENTIATION OF SLIME MOLDS<sup>3</sup>

There has been a renewed interest in plasmodium- and pseudo-plasmodium-forming organisms in the last few years, and recent work with these plants is well worthy of inclusion here. As a fairly well-defined group, it seems best to treat them as such, rather than to try to include them piece-meal in other sections of this review. They are unique in that their growth phase is separate from the reproductive.

<sup>3</sup> The helpful suggestions of Kenneth B. Raper have made it possible to include the Slime Molds in this review.



The two groups of slime molds mentioned above are classified as follows (121): (a) Myxomycetae, those in which the vegetative body is a free-living single large multinucleate protoplast, or plasmodium, that develops into a fruiting body of definite form, and (b) Acrasieae, those in which there is a pseudoplasmodium that results from an aggregation of many small uninucleate protoplasts, or myxamoebae, which though retaining their individuality, combine to form a fructification of definite form. The latter during their vegetative period are amoeba-like in their feeding and growth habits, but subsequently give rise to fruiting structures definitely plant-like in character.

Raper (122, 123) has studied substrate requirements in detail for certain Acrasieae, as well as the influence of three bacterial associates, *Escherichia coli*, *E. communior*, and *Pseudomonas fluorescens*. Growth and development of the slime mold *Dictyostelium discoideum* were governed by the pH of the bacterial colonies into which it was introduced. The extreme range was from about pH 4 to 8.5, with the optimum at 6 to 6.5. Culture conditions had to be more nearly optimum for fruiting than for vegetative growth. The second paper (123) is an analysis of organization and behavior of *Dictyostelium* under optimum conditions. Raper & Thom (124) have determined the behavior of different species of *Dictyostelium* when intermingled during their vegetative growth, and find that although different species of myxamoebae may vegetate together, they tend to fruit separately. It was possible to follow cells of certain species in their final behavior by feeding them red-pigmented bacteria, the pigment of which they were unable to digest; thus the fruiting bodies of such species were red, whereas the fruiting bodies of other species were colorless. Grafting was possible, and grafts between individuals of the same species formed a permanent union in the fruiting body, whereas temporary unions or no union at all usually occurred when different species were grafted. Certain intermediates obtained suggest hybrids, though they apparently are physical mixtures of different species and no genetic change is involved.

In a study of nutritional requirements of the plasmodium-forming organisms (Myxomycetae), and using bacteriological techniques as criteria for determining culture purity, Cohen (125) has found that plasmodia normally feed upon living microorganisms (bacteria, yeasts, and fungi), though they can also utilize auto-



lyzed yeast. They are unable to use oatmeal or other vegetable media directly, as had been previously reported by others.

Gray (126, 127) has determined the effect of certain environmental factors upon the growth and reproduction of slime molds. The first paper reports that fruiting rhythms are markedly affected by light: nonpigmented forms fruit equally well in light or darkness, whereas yellow-pigmented types fruit only after exposure to light. Light of 300 to 550  $\mu$  was effective in inducing fruiting. The second paper reports that pH and temperature are closely related and interdependent in influencing fruiting. At a constant pH, fructification is delayed if the temperature rises, but relatively fewer cultures succeed in fruiting. At a constant temperature, maximum fructification is obtained at pH 3, and decreases as the pH rises. The necessity of light for fructification in yellow-pigmented forms is not supplanted by increasing the acidity or by lowering the temperature. Certain characteristics of the mature sporangium were found to vary markedly at different temperature levels.

Gray (128) has studied the effect of full radiation from a mercury vapor lamp on pigmented and nonpigmented species of *Phy-sarella*; it is reported that the pigmented species are more resistant, thus indicating a shielding effect.

The early literature on slime molds, up to 1939, has been reviewed by Martin (129), and the developmental history of the Dictyosteliaceae has just been reported by Raper (130).

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DEPARTMENT OF BOTANY  
CONNECTICUT COLLEGE  
NEW LONDON, CONNECTICUT



## ENERGY METABOLISM

BY WILLIAM H. CHAMBERS, EPHRAIM SHORR,  
AND S. B. BARKER

*Departments of Physiology and Medicine, Cornell University Medical College, and  
the New York Hospital, New York City, New York, and the*

*Department of Physiology, University of Tennessee  
College of Medicine, Memphis, Tennessee*

A departure from previous custom has been made to include a review of the energy metabolism of organs and isolated tissues with that of the whole organism. The articles reviewed are taken from the American literature for the year ending October 1, 1941, and from the foreign publications which have become available during this period.

### GENERAL ASPECTS OF METABOLISM

*Basal metabolism standards.*—Some progress is reported on the puzzling question of the relative importance of race, climate, diet, and other possible factors in influencing the basal metabolism of inhabitants of tropical countries. European soldiers in Singapore were examined by MacGregor & Loh (1), some within six months of arrival, another group after two and a half years of residence, and some at frequent intervals. Generally the basal metabolism fell during the first year of residence and then remained fairly constant. Considerable individual variation was found since 40 per cent of one group showed no significant decrease. The soldiers lived under barracks routine and received 129 grams of protein and 4000 calories daily, hence it was concluded that the fall in metabolism was due to climatic rather than occupational or dietetic factors.

Natives of Bombay may have a B.M.R. as low as —16 per cent according to the earlier observations of Niyogi and co-workers (2). In a recent study (3) of medical college groups the low metabolism could not be definitely related to protein intake, creatinine coefficient, changes in temperature or humidity, or state of nutrition. It was therefore thought that the racial factor was most important.

Information regarding the influence of age, sex, and puberty in the formulation of basal metabolism standards has been obtained by Webster, Harrington & Wright (4) from the determination at frequent intervals of the respiratory metabolism of a group of boys and girls during adolescence. The gradual decrease in calories per square meter between the ages of ten and sixteen in



individuals of both sexes substantiates the results of earlier investigators who used the group sampling method. Data on the boys show the closest agreement with Bierring's curve, those for the girls with Kestner & Knipping's values. The sex difference is present at ten and more marked at fifteen years of age. No evidence is found of an increase in basal metabolism at puberty.

*Environmental temperature.*—The recently developed interest in heat loss from the body continues to yield important results concerning physiological reactions to environmental temperature. In studies of relative heat production and heat loss with a new and more accurate apparatus, Winslow, Gagge & Herrington (5) have emphasized the difficulties encountered in a quantitative measure of temperature changes or heat storage in the whole body. Observations were made over air temperature ranges of about 16° to 48°C. and wall temperatures of about 14° to 41°C. The changes in heat stored in the body were computed in two ways, (a) from skin and rectal temperatures, weighted in a ratio of 1:2, and (b) by subtracting from the determined metabolism the sum of the heat loss by evaporation, radiation, and conduction. As the operative temperatures [combined environmental temperature effects (6)] fell below 26°C., the difference between the two methods of calculation became increasingly greater, the error from skin and rectal temperatures amounting to 40 cal. per sq. m. per hr. in one experiment at 20°C. even though a fairly steady state had been attained.

Standard operative temperature is defined by Gagge (6) as the expression in a single temperature scale of the combined effect of the radiant temperature, the ambient air temperature, and the air movement. These are the physical properties of the environment, exclusive of evaporation and humidity, which govern heat loss from a warm body by radiation and convection. Equations are given for calculating the operative temperature from the skin temperature and the measured heat loss divided by 5.2 (the cooling constant  $K$  in Newton's Law), or from the skin, wall, and air temperatures and the air movement.

The complete data of the studies on eight women in the Sage calorimeter over a temperature range of 22° to 35°C. have been reported by Hardy, Milhorat & DuBois (7). In comparison with two men previously studied, the most striking sex difference is the "chemical regulation" in women between 27° and 32°C. The point of lowest metabolism in the women averages about 4 cal. per sq.



m. per hr. or 12 per cent below that of the men at 30° to 32°C. Below 27°C. the heat production of the women and the men is the same although the heat loss of the women is less by 3 to 4 cal. per sq. m. per hr. In the cold zone, skin temperature, vaporization, and conductance are all lower in the women. The weighting of skin and rectal temperature changes for estimating heat storage in the body is discussed.

Exposure to very cold temperatures as in the hypothermia treatment of patients may cause a rise in metabolism of two or three times the basal rate, when a low rectal temperature of 30°C. is maintained over long periods of time. In the observations of Dill & Forbes (8) the high metabolism could probably be accounted for by muscular activity: shivering, voluntary activity, and a muscular rigidity of unknown origin. Ketonuria and low respiratory quotients even after glucose administration suggest a high fat metabolism. A detailed study of the effects of low temperature on the respiratory properties of the blood shows that the regulation of acid-base balance remains effective despite a low alkaline reserve, acidosis, and hyperventilation. The authors point out that a body temperature of 20°C. is fatal to most nonhibernating mammals and recall Tait's hypothesis that the solidifying temperature of the body fat is significant in respect to maintenance of function at low temperatures. In most of the nonhibernating mammals the solidifying temperature is above +15°C. whereas in the marmot it is about -15°C.

The average B.M.R. is significantly lower at an "effective temperature" of 70° to 72°F. than at the low tropical temperature of 78° to 80°F. in Radsma's study of nineteen individuals (9).

The effect of surface insulation against cold is shown by Lee, Colovos & Ritzman (10) by comparing at air temperatures between -12° and +21°C. the skin temperatures of the sheep, goat, and pig with their previously determined metabolic rate. The sheep maintains a fairly uniform skin temperature without increasing heat production even when the air temperature falls to 0°C., whereas the goat's metabolism increases when the air temperature falls below 20°C. and thus keeps the skin temperature at about 30°C. Due to a poor coat of hair the skin temperature of the pig fluctuates with the environmental temperature, but the insulating layer of fat protects against stimulation of increased heat production down to an air temperature of 12°C.



The observations of Day (11) on the heat loss of sleeping children, associated with a fall in rectal temperature, suggest that the physiologic thermostat becomes set at a lower level of body temperature during sleep.

Contrary to the results of earlier investigators, Barott & Pringle (12) report that the hen exhibits a fall in oxygen consumption as the environmental temperature is lowered from 60°F. to 50°F. Likewise they found a fall in sensible heat loss from the body and in the elimination of respiratory water under these conditions. This extraordinary reaction to cold which has no counterpart in mammalian metabolism needs further investigation. No data are given concerning surface and internal body temperatures. Between 60° and 95°F. the expected changes in calculated and direct heat production are found with the minimum metabolism at 78°F. Respiratory quotients average 0.70 about twenty hours after feeding.

*Hibernation.*—Kayser (13) has continued his extensive studies of the metabolism of hibernating species which were reviewed last year (14). During hibernation the respiratory quotients of all species—marmots, spermophiles, dormice, and bats—are in the range of 0.71 and thus agree with those found by Benedict & Lee in marmots. The hibernating heat production at an environmental temperature of 10°C. is uniform at about 0.1 cal. per kg. per hr. in the species weighing over one hundred grams, although a species difference is seen if they are compared on the surface area basis. Determinations of direct calorimetry on the dormouse were unsuccessful. The oxygen consumption of the hibernating marmot and spermophile is definitely higher than that of cold-blooded species of a similar weight at the same environmental temperature.

The brown axillary fat of hibernating woodchucks and ground squirrels has been extracted with peanut oil by Hook (15). On intraperitoneal injection of the extract into white rats, a fall in heat production may occur within one hour or after one or two days. These results are in general agreement with an earlier report by Wendt. Of interest in this connection is the finding by Sweet & Hoskins (16) of a very high concentration of androgen in the brown fat of nonhibernating woodchucks.

*Specific dynamic action (S.D.A.).*—For a study of the S.D.A. of amino acids (glutamic, alanine, glycine, tyrosine, aspartic, and asparagine) Kriss (17) has revived the method of Kellner &



Armsby. The respiratory metabolism of rats is measured for seven hours following the ingestion of a basal meal, when the animal is on a maintenance ration. The amino acid supplement is then added to the diet for eight days and the metabolism determined as before. The basal maintenance metabolism is determined again and the average of the two serves as a base value for calculating extra heat production. Nitrogen, carbon, and energy balances for these experiments have been published previously. All of the supplements cause an extra heat production above the maintenance level, which is different for each amino acid. If calculated per millimole of amino acid metabolized, tyrosine has the highest S.D.A. and glutamic acid is second. Statistical analyses of the data show a close correlation between the extra heat and the metabolizable energy of each amino acid whereas there is no direct correlation with the nitrogen metabolism. Whether or not this is inherent in the Kellner & Armsby method remains to be determined by direct comparison with the more commonly used Rubner method. It should be noted that the basal metabolism in the Rubner method as used in dog experiments is determined in a postabsorptive but not a fasting state, since the experiment is performed in the period between two regular daily rations. In this connection the author discusses the evidence for a fasting S.D.A. of endogenous metabolism. In a brief report of calorimetric studies on four steers, Forbes & Swift (18) calculate a value for the theoretical minimum heat production for the fasting state.

Contrary to the above results, the observations of Herrin (19) have led him to emphasize the importance of the nitrogenous part of the amino acid, in agreement with the early work of Grafe and of Lundsgaard. The effect of sodium and ammonium acetate and lactate is compared with that of glycine and alanine in human subjects.

Histidine is placed by Eaton & Doty (20) in the list of amino acids which yield extra heat on intravenous administration to the dog. The S.D.A. amounts to about 9 calories per gram of extra nitrogen excreted. This is about one half that of glycine on a weight basis or twice as much on the basis of millimoles deaminized. Histidine is metabolized more rapidly than arginine and has a 50 per cent greater calorogenic effect.

The S.D.A. of oleic acid is not significantly affected by a fat diet in normal rats but in depancreatized rats a fat diet for three



days elevates the calorogenic action of the fatty acid. Ring (21) suggests that the depressing action of injected cortin in these experiments is due to increased glycogen stores.

Rynbergen, Chambers & Blatherwick (22) report that a diminished oxidation of ingested fructose in two fructosuric subjects accompanies the absence of the normal rise in blood lactate. The S.D.A. of fructose in one subject was within the normal range, while in the other subject with a greater impairment in fructose oxidation, the extra heat was about 25 per cent lower.

*Food materials.*—Although vitamins A and C added to the stock diet have no effect on the basal metabolism of normal rats, Belasco & Murlin (23) find that either vitamin is effective in lowering the hypermetabolism following thyroid administration. The opposite effect is seen in the experiments of Mosonyi & Kézdi (24) on guinea pigs lacking vitamin C. The increase in oxygen consumption which appears during the last fifteen days of a fatal scurvy can be prevented by thyroidectomy or by castration. If the caloric intake of rats is doubled by exposure to cold, the thiamin requirement for growth is not increased, since one half the thiamin concentration in the food is adequate, according to the experiments of Mills (25).

A similar increase in B.M.R. and reduction in food utilization is found by Kleiber, Boelter & Greenberg (26) in rats with a deficiency in either magnesium or calcium. However, hypertrophy of the thyroid and adrenal glands occurs only in the magnesium-deficient rats. Whether the food is given to the rat in one or five meals per day does not affect the metabolic rate on the following day (27).

As much as 30 per cent of the calories fed to a premature infant on the standard diet of about 120 cal. per kg. per day may be lost in the form of fecal fat. The observations of Gordon & McNamara (28) indicate that the majority of full-term infants lose less than 10 cal. per kg. per day in the feces. The effect of reducing fat intake on gain in body weight is discussed.

The extent of ketone body oxidation in the intact body is seen in the experiments by Wick & Drury (29). The utilization of injected sodium  $\beta$ -hydroxybutyrate at a blood concentration of about 80 mg. per cent would account for 85 to 90 per cent of the total oxygen consumption of the rabbit.

*Exercise.*—During a training period of twenty-six weeks, the



subjects observed by Robinson & Harmon (30) maintained a constant basal metabolism. Oral administration of gelatin in the middle of the training period did not alter the oxygen debt or any of the other muscular functions that were studied. In another series of controlled human experiments by Karpovich & Pestrecov (31) there was no evidence that gelatin increases muscular efficiency although the psychological effect of gelatin substitutes was apparent.

The maximum work which can be accomplished by human subjects is increased by the addition of vitamin B<sub>1</sub> to the diet, according to the observations of Droese (32), although metabolic rate and efficiency are not influenced. In B<sub>1</sub> hypovitaminosis a compound containing B<sub>1</sub> and glucose was effective.

In measuring respiratory metabolism during work, Matthes (33) notes significant changes in R.Q. when respiratory resistance is varied.

*Drugs.*—Caffeine alkaloid stimulates hyperventilation and thus elevates the R.Q. for about thirty minutes. In these experiments of Haldi *et al.* (34) a compensating retention of carbon dioxide occurs in the following seventy-five minutes. The finding of increased oxygen consumption agrees with the results of previous investigators.

Statistical analyses by Griffith, Emery & Lockwood (35) of the metabolism of eighty-four unselected cats under chloralose anesthesia and with a cannula in the trachea show lack of correlation between metabolic rate and either body weight or surface area. Allowing for the fall in body temperature raises the metabolism from -4.6 per cent to +7 per cent.

#### GLANDS OF INTERNAL SECRETIONS AND HORMONES

*The thyroid apparatus: animals.*—Meyer and his associates have continued their provocative studies on the activity of fractions of thyroid gland substance. Their previous work (36) had dealt with the separation, by chemical means, of two fractions from normal sheep thyroid, one of which had a predominant effect on the basal metabolism, the other on the heart rate of the thyroidectomized rat.

The more recent study of Meyer & Danow (37) meets the objection that the previous results may have been due to artifacts resulting from the chemical procedures employed. They fed thyroidectomized rats with fresh thyroids from normal rats and rab-



bits, some of which had received iodine. The thyroids from animals which had not been fed iodine raised the B.M.R. significantly without elevating the heart rate. Thyroids from iodine-fed animals not only raised the B.M.R. but elevated the heart rate to a disproportionately high degree.

Meyer & Thompson (38) carried out a similar experiment employing the fresh thyroid of man and of the pig. Fresh thyroids from normal pigs had a relatively slight effect on the heart rate as compared with the effect on the B.M.R. of the thyroidectomized rat. This was also true for the fresh thyroid gland from the normal human, whereas glands from patients with Graves' disease who had received iodine stimulated the heart rate to a greater degree, and frequently in excess of what would be proportional to the increased B.M.R. A single gland from a patient with Graves' disease who had not received iodine, had a weaker action on the heart rate.

Many phenomena encountered in disturbances of the thyroid apparatus in man are compatible with the concept inherent in these experiments that the thyroid may elaborate more than one active principle, particularly in disease. Among these are the frequently observed dissociation in Graves' disease between the B.M.R. and the heart rate, and the ability of iodine to abolish the creatinuria of Graves' disease without influencing the B.M.R. (39).

Another type of iodine effect was reported by Ring (40). The administration of 25 mg. of sodium iodide daily to normal rats had no effect on the B.M.R. at room temperature, but survival was low at 4°C. It was suggested that the iodine may have rendered the thyroid inactive and hence less able to meet the requirements of heat production for survival at these low temperatures. As much as 400 mg. of sodium iodide per day did not influence survival at room temperatures; its discontinuation was followed by a lowered basal metabolism.

Fleischmann, Schumacker & Wilkins (41) studied the effects of total thyroidectomy on the serum cholesterol and B.M.R. of rabbits. This procedure was followed by a sharp rise in serum cholesterol (average 171 per cent) which became stabilized after about twelve weeks at +80 per cent (average) above basal level. The B.M.R. fell gradually to reach a level of about -40 per cent in the sixth week. The thyroidectomized rabbit was found very sensitive to a single injection of thyroxine as regards the B.M.R., urinary



creatine, and serum cholesterol. As in hypothyroidism in children and adults, there was much overlapping of the serum cholesterol values of normal and hypothyroid animals. Hypothyroid rabbits were more prone to wide fluctuations in serum cholesterol levels than were normal animals.

Although thyroidectomy results in higher levels of blood cholesterol and total blood lipids, MacKay & Sherrill (42) were unable to find evidence of increased fat deposition in thyroidectomized rats. On the contrary, the fat content of these animals averaged 6.4 per cent as compared with 31 per cent in the controls. The fat content of normal rats fed thyroid was also lowered.

Sure, Ford *et al.* (43) found that hyperthyroidism induced in rats by thyroxine resulted in an increased output of urinary nitrogen, a marked creatinuria with a reduction in preformed creatinine, increased excretion of ammonia and uric acid, and a reduction in the excretion of allantoin. A marked hyperuricacidemia was observed. Neither vitamin A, ascorbic acid, nor glycine prevented the marked reduction in muscle or heart creatine in these hyperthyroid rats. The probable relation of this defect in creatine metabolism to the muscle weakness and degeneration in Graves' disease has been pointed out (44).

Boettiger (45) continued his studies on the metabolism and growth of dwarf mice. Thyroxine increased the basal metabolism and raised the growth curve of this strain of mice over the untreated controls. Similar changes were also obtained when the animals were maintained at higher environmental temperatures. Apparently this effect is dependent on a nonspecific stimulation of metabolic activity.

The influence of environmental temperatures on the morphology of the thyroid and adrenals of the rat was studied by Bernstein (46). The thyroid epithelium was found higher in winter and lower in summer. The reverse was true for the adrenal cortical sudanophil substance. That these changes are a response to the extremes in environmental temperatures at these seasons appears likely from their production by experimentally altered thermal environments. These morphological changes are related, it is suggested, to the maintenance of a constant body temperature.

Mansfeld, and Mansfeld & Meszaros, contributed a series of papers on the relation of the thyroid to the heat-regulatory mechanisms. From a study (47) of the means by which thyroxine pre-



vents the fall in body temperature of guinea pigs which otherwise results from the vasodilatation caused by novocaine, they postulate an influence of thyroxine on heat loss by direct action on vasomotor centers in the cord. Their experiments (48, 48a) would also involve the thyroid in the humoral control of heat production. Serum from animals whose body temperature had been lowered 2° to 3°C. by chilling raised the metabolic rate of excised muscle and of the intact animal; serum from animals whose temperature had been elevated 1° to 2°C. by warming had the opposite effect. Serum from similarly treated thyroidectomized animals was without effect. Animals injected with thyroxine yielded serum which behaved like that from chilled animals. They also claim (49) the isolation from the thyroid of a principle antagonistic to thyroxine and which they regard as responsible for the depression of metabolism by serum from warmed animals.

Thyroid feeding had no effect on the oxygen consumption of goldfish according to Etkin, Root & Mofshin (50).

*The thyroid apparatus: man.*—The problems encountered in the diagnosis of hypothyroidism have stimulated a number of studies, particularly on children, designed to evaluate the criteria ordinarily employed. Among the more important laboratory observations are the levels of the B.M.R. and blood cholesterol, the urinary excretion of creatine and the retention of ingested creatine. Wilkins, Fleischmann & Block (51, 52) have studied these factors in hypothyroid children. The B.M.R. per se was not found reliable: while a majority of hypothyroid children were low, several were normal, and many normal obese children had equally low basal rates. They found a wide range of blood cholesterol values in normal children (98 to 308 mg. per cent). While hypothyroid children were frequently above this level, there was considerable overlapping and normal values were found in severe hypothyroid states. As regards creatinuria, the absence of which in childhood is frequently stated to be pathognomonic of hypothyroidism, they found an excretion of 0.6 to 7.8 mg. per kg. per 24 hrs. in the normal child as compared with 0 to 3.8 mg. per kg. per 24 hrs. in hypothyroidism, but again with too much overlapping to be specifically diagnostic. Creatine tolerance tests gave the same results for both groups.

According to their studies, more reliance can be placed on the response of these various criteria to thyroid medication, the changes



in blood cholesterol being most significant. The fall in cholesterol is much more marked in hypothyroid children (117 to 385 mg. per cent) than in normals (0 to 76 mg. per cent). The creatinuria induced by thyroid feeding is less helpful, since it is shown by 42 per cent of normals given one-half grain daily and 77 per cent given two grains.

Wilkins & Fleischmann (53) point out that confirmatory evidence can be obtained from blood cholesterol changes on discontinuation of thyroid therapy. They employed as an additional diagnostic procedure the effect of injections of thyrotropic hormone and desiccated thyroid feeding on creatinuria (54). Hypothyroid children failed to develop a creatinuria after thyrotropic hormone, but creatinuria followed thyroid feeding. Normal children had a positive response to both.

Radwin, Michelson *et al.* (55) regard the total lipid content of the blood as more significant than the total cholesterol level for the diagnosis of hypothyroidism in children. They found the total lipids to be decidedly elevated over the normal range in all hypothyroid children. There was, however no strict proportion between the height of the total lipids and the severity of the hypothyroidism. Tobias & Stockford (56), in their analysis of the merits of the B.M.R., blood cholesterol, and carpal development as a measure of the "metabolic speed" in children, found blood cholesterol the most reliable. From an analysis of 404 cases, Hurxthal & Simpson (57) conclude that although a considerable percentage of adults with hypercholesterinemia had thyroid insufficiency, there is much overlapping with the normal range and the change with thyroid medication is more valuable than the pretreatment level. They suggest a curve for the normal values which rises with increasing age.

Another metabolic correlate of hypothyroidism has been studied by Talbot, Hoeffel *et al.* (58). They found the serum phosphatase of infants and children with hypothyroidism to be abnormally low, and to be restored to normal by adequate thyroid therapy. The range for the normal child is 5 to 14 Bodansky units (average 7), and for untreated hypothyroid children, less than 4.5 units (average, 2.5). These low values would seem to mirror the delayed skeletal development of the juvenile hypothyroid.

Two studies have dealt with the relation of blood iodine levels to the B.M.R. in man. McClendon & Foster (59), measuring "thy-



roid hormone iodine" in blood and tissues, found 1 mg. of thyroxine in the body of a 65 kg. adult for each  $\mu\text{g.}$  of thyroxine iodine per 100 cc. of blood. A good correlation was found between the level of the B.M.R. and the amount of thyroxine iodine in blood. For every 10 per cent increase in B.M.R. an increase of 1  $\mu\text{g.}$  of thyroxine iodine per 100 cc. of blood was observed and, by calculation, of 1 mg. of thyroxine in the tissues per 65 kg. of body weight. A B.M.R. of  $\pm 0$  per cent would be maintained by a total of 5 mg. of thyroxine distributed throughout the tissues. This compares with the figure of 12 to 14 mg. of thyroxine arrived at by Boothby (60) from a consideration of the calorogenic effects of thyroxine in human myxedema.

Phatak, Zener & David (61) have studied the relation of total blood iodine to the well-known elevation of B.M.R. during pregnancy in the human. As compared to the normal level of from 8 to 12  $\mu\text{g.}$  per 100 cc. blood iodine levels of from 15 to 17  $\mu\text{g.}$  per 100 cc. were found throughout pregnancy. At term the blood iodine rose to 20  $\mu\text{g.}$ , and, by the sixth week postpartum, fell to 14  $\mu\text{g.}$  The increase in blood iodine during pregnancy was accompanied by an elevation in the B.M.R. to +26 per cent by the second trimester, a level which was maintained throughout the rest of the pregnancy. By the sixth week postpartum, the B.M.R. had fallen to +14 per cent. In a second series of pregnant women who had received iodine throughout their pregnancy, the B.M.R. remained between +10 and +15 per cent. The higher metabolic rates in the women not receiving iodine are regarded as a consequence of an increased stimulation of the thyroid during pregnancy. This strain can be relieved by the administration of iodine. The abundant evidence of strain on the thyroid apparatus of animals and man during pregnancy, and its relief by iodine, would appear to justify the prophylactic routine use of iodine in this state.

In a study of the calorogenic effects of thyroid substance in obese subjects, Handelsman & Gordon (62) found that, except in the small percentage with hypothyroidism, calorogenic effects were irregular and did not occur in the majority of subjects, even with large doses. Despite the absence of an increased metabolism, thyroid substance occasionally accelerated weight loss, possibly by its diuretic action.

Blotner & Cutler (63) did total thyroidectomies in three cases of diabetes insipidus, one idiopathic and two of postencephalitic



origin. In the two latter cases, a definite thyroid insufficiency ensued and was accompanied by a relief of the polydipsia and polyuria. Subsequent administration of thyroid reestablished the polyuria and polydipsia at lower than original levels. The mechanism of relief, whether diminished metabolism, removal of diuretic effect of thyroid, or the circulatory changes of hypothyroidism, was not apparent from the data.

*Ovaries and ovarian hormones.*—Enough data have accumulated to indicate that the ovarian hormones may participate in the regulation of heat production. Studies extending back more than a century have established the existence of a periodic variation in the basal temperature of women during the menstrual cycle. Barton (64) has reviewed the subject exhaustively and reported her own observations. During menstruation, the rectal temperature remains at a low level, with a further decline three days later. This, the lowest level of the temperature cycle, occurred most frequently on the tenth day after the onset of menstruation and persisted for about three days. According to Rubenstein (65) it is correlated with the presence of the ovulative smear. Then occurred a gradual rise over a period of twelve days to a peak which was maintained for about three days, after which there was a decline just before the onset of the next period. During the early months of pregnancy, Barton, in agreement with other workers, found the temperature curve to persist at the higher premenstrual levels and to be devoid of significant cyclic alterations. The average variation in rectal temperature during the menstrual cycle was  $0.6^{\circ}\text{F}$ .

Cyclic variations have also been found in the basal heat production during the menstrual cycle (66). The extent of the deviation in B.M.R. is so small (2.7 to 6 per cent) that a statistical analysis of the data has been necessary. From many careful studies it appears that there is a tendency for the B.M.R. to be lowered during the menstrual period and that there is usually a second low point at about the middle of the intermenstrual period. The highest metabolic rate occurs in the premenstrual period. These are the general trends. The additional observation has been made by Rubenstein (65) that the low intermenstrual point coincides with the ovulative vaginal smear.

By means of the more exact methods provided by the Sage calorimeter (see page 140), Hardy, Milhorat & DuBois (7) have demonstrated another mechanism for heat regulation, which the



ovarian hormones may significantly influence, namely, the adaptation to the warmer temperature zones. The depression in heat production above 27°C. found in menstruating women is absent in men.

These phenomena will require a detailed analysis of the factors responsible for their production. During the past year several papers have appeared in which such an analysis in animals and man has been attempted.

Sherwood and associates found that estrone, estradiol, and stilbestrol were effective in decreasing the B.M.R. of intact or ovariectomized female rats made hyperthyroid by thyroid feeding. He now reports the same findings on thyroidectomized-castrated male rats (67). Normal and thyroidectomized rats with a hypermetabolism (+60 per cent and +88 per cent respectively) induced by feeding 1 gm. of desiccated thyroid per kg. for three days had a return to the original basal metabolic rate in 6.5 to 7.5 days. The thyroidectomized-castrated animal under the same conditions had a greater increase in metabolism (96 per cent) and required sixteen days for the restoration of the original B.M.R. The administration of estrogen to the thyroidectomized-castrated group reduced the calorogenic effect of the administered thyroid to 19 per cent, and permitted a return to the original B.M.R. within 5.3 days. Sherwood (68) also found that estrogen, administered to thyroidectomized rabbits whose basal metabolism was increased to 70 per cent above their hypothyroid level by desiccated thyroid, brought about a return of the original level of B.M.R. in 16 days as compared with 31 days in the control group. The evaluation of experiments of this type must be qualified by a consideration of the dosage level of estrogenic hormone employed. The comparable daily dose of estrogen in the human would be approximately 2,000,000 I.U. (one Human Unit = 15,000 to 25,000 I.U.). The implications of these experiments for the heat-regulating role of estrogens in the normal economy of the organism would be greater were more physiological amounts of estrogens employed.

The relation of hypothyroidism to the estrous cycle in guinea pigs has been investigated by Williams, Phelps & Burch (69). They found that hypothyroidism may give rise to a disturbance in ovarian function, but that the hypothyroidism must be marked to produce significant changes.

Carpenter (70) was unable to find any significant variations in



vaginal temperatures during the menstrual cycle of two gibbons; this finding is in contrast to the cyclic alterations observed in the menstrual cycle of women.

The influence of estrogenic hormones on the B.M.R. of castrated women was reported on by Collett, Reed *et al.* (71). Confirming their previous studies, they found that six daily doses of 500 I.U. of estrone intramuscularly raised the B.M.R. by 10 per cent, whereas six daily injections of 1,000 I.U. caused an elevation of 5 per cent. By the oral route, 1,000 I.U. of estrone produced a rise of 10 per cent, 2,000 I.U. of 5 per cent in the B.M.R. They suggest that the estrogens might be assayed in the human by their effect on the B.M.R. It is interesting that as little as 500 I.U., which represent about one-twentieth to one-thirtieth of the estrous dose in the human, should cause a rise in the B.M.R. of as much as 10 per cent. The relative potency of estrone by the oral and intramuscular route as indicated by this method of assay is out of harmony with results obtained with more specific methods such as the vaginal smear, which reveals a far greater loss of potency by the oral route (72).

Hamblen, Pullen & Cuyler (73, 74) made a correlation of B.M.R. and defects in reproductive function. In sterile men with defective spermatogenesis, semen specimens from those with B.M.R. levels lower than minus 15 per cent were rather better than from those with more normal rates. Women with a variety of menstrual disturbances, showed rather less qualitative impairment of menstrual function, as judged from endometrial biopsies, in the group with B.M.R. values below minus 10 per cent than in those in the normal range. Data were lacking, however, which would relate the lower B.M.R. levels to actual thyroid insufficiency.

*Androgens and heat production.*—Evidence is accumulating that the androgenic hormones may also influence heat production in man. Calorigenic effects of the naturally occurring androgen, testosterone, and its propionic ester, have been reported by a number of observers to follow their prolonged administration to eunuchoid males (75, 76). On the other hand, the energy metabolism of castrated male dogs has been found to be uninfluenced by these hormones (77).

Additional evidence of the action of androgens on heat production has been contributed by McCullagh & Rossmiller (78), and by McCullagh, Jones *et al.* (79). They employed the partially syn-



thetic methyl testosterone,  $\Delta^4$ -androstene-methyl-17-ol-17-one-3, which differs from the natural androgens in that it is capable of inducing androgenic effects when administered orally; the natural androgens lose so much of their activity by this route as to make their oral administration impractical. The administration of 50 to 300 mg. of methyl testosterone to hypogonadal males was followed, after three or more weeks, by elevations in the B.M.R. of from 12 to 54 per cent. This elevation was roughly proportional to the dosage employed, 50 mg. producing an average rise of 15 per cent, 200 mg. an average rise of 24 per cent. No further rise was observed with larger amounts. The hypermetabolism appeared to differ from that seen in hyperthyroidism. It was not accompanied by tachycardia, palpitation, hyperpiesis, or increased sweating. There was no correlation between the changes in basal heat production and blood iodine and cholesterol levels. In spite of the increased activity manifested by the subjects, there was an increase in weight and muscle mass. As in the case of testosterone and its esters, methyl testosterone was found to exert a sparing action on the urinary excretion of nitrogen, phosphorus, potassium, sulphur, and water. A qualitative as well as quantitative effect on metabolism was suggested by the fall in the R.Q. of five of nine subjects. The very low R.Q. values (e.g., 0.690) observed in some cases warrant further studies of this aspect to validate these unusual results. The circulatory adjustment of the hypermetabolism induced by methyl testosterone was incompletely studied. The circulation time was found to vary with the B.M.R., decreasing with a rising B.M.R. and increasing again on discontinuation of therapy. More extensive studies of the circulatory response to this type of hypermetabolism should prove interesting.

The extent of the increase in basal heat production with methyl testosterone appears to be somewhat greater than that observed with testosterone or its esters. The suggestion may be advanced that the changes in chemical structure which enable the steroid hormones to suffer less inactivation than the natural hormones when administered orally, may, for the same reason, permit their accumulation in the body in higher concentrations than is the case with the natural hormones. As a consequence, an exaggeration of the effects produced by the naturally occurring hormones might be anticipated.

*Pancreas.*—Dohan, Chambers & Fish (80) carried out studies



on diabetes induced in dogs by the injection of anterior pituitary extracts. The development of the diabetic state was associated with an increase in basal oxygen consumption of from 10 to 20 per cent. This could be reduced by the administration of insulin. No increase in oxygen consumption followed the administration of glucose alone. Meat feeding caused a marked increase in oxygen consumption. Both foodstuffs yielded essentially diabetic R.Q. values, except when insulin was also administered, in which case the R.Q. values were elevated as in the normal dog. There was a definite correlation between urinary nitrogen excretion and the level of oxygen consumption.

*Pituitary.*—Feinstein & Gordon (81) investigated the elusive metabolic principle of the pituitary, using a liver extract as a control. Small immediate rises in the B.M.R. were observed in humans and in rabbits with intact thyroid gland, but the results were erratic in both groups. In view of Teague's (82) report that metabolic stimulation is obtained with pituitary extracts after treatment with acid and after tryptic digestion, the existence of a specific metabolic principle of the pituitary remains doubtful.

*The adrenals.*—Brownell & Hartman (83) studied the influence of the adrenal cortical hormones on B.M.R. and the specific dynamic action (S.D.A.) of carbohydrate and fat. Treatment with cortin, the sodium factor, desoxycorticosterone, or sodium salts, which was adequate to keep adrenalectomized dogs in good condition, supported normal B.M.R. levels. Even though the animals were maintained in good condition by these substances, there was a significant delay in the development of the S.D.A. after both carbohydrate and fat. This was more marked after desoxycorticosterone. Sugar tolerance curves suggested that delayed absorption might explain the slow development of the S.D.A. after this foodstuff.

Asmussen, Wilson & Dill (84) confirmed their previous observation that epinephrine (1 mg. intramuscularly) increased the oxidation of carbohydrate during muscular exercise in man. Their latest experiments were prolonged sufficiently to permit the blood lactic acid to return to normal values, in order to eliminate the possibility that the high R.Q. values after epinephrine might be due to the blowing off of carbon dioxide as a result of the rapid initial increase in blood lactic acid produced by epinephrine.

*The parathyroids.*—Chandler & Pickett (85) found the oxygen



consumption of the albino rat to be uninfluenced by complete parathyroidectomy. However, there were no studies of calcium or phosphorus metabolism carried out to validate the existence of parathyroid insufficiency in the animals studied.

#### METABOLISM OF TISSUES

*Summated tissue metabolism.*—Fifteen years ago Grafe and Terroine independently noted that homologous tissues excised from mammals ranging in size from the mouse to the ox had essentially the same *in vitro* respiration per unit weight. Since respiration of the whole organism on a weight basis was known to fall off markedly over such a series of animals, these authors concluded that some factor inherent in the whole animal organization must exert a depressant regulatory influence on tissue metabolism *in vivo*. Many results scattered throughout the literature of tissue respiration suggest that the data on which this conclusion rested were not true [for instance, Marsh (86), and Richardson (87)]. In 1939, Field, Belding & Martin (88) found the total of the metabolism of the rat *in vitro* to be 66 per cent of that *in vivo* when oxygen consumption was extrapolated back to the time of removal of tissues. In a preliminary report on the dog, Martin & Fuhrman (89) stated that addition of the tissue values accounted for 74 per cent of the resting metabolism of the dog. The values obtained on the individual tissues are probably somewhat too high, due to extrapolating back to time of excision of tissues, through a period of metabolism enhanced by the artifact of high concentration of lactate (and other intermediates) produced during preparation of the tissues. It is highly probable that there is an organizational factor, but concerned with stimulation of the respiration of the tissues rather than with the restraining influence postulated by Grafe and Terroine. Maintenance of circulation, respiratory movements, and muscle "tone" can be considered to require an increase of at least 25 per cent over the strictly resting condition of the excised tissues (90). Hormonal influences must also be considered as playing a part.

*Conditions in vivo.*—Considerable interest has been shown in metabolic problems related to the thyroid. Spirtes (91) reported that the feeding of desiccated thyroid to guinea pigs caused no apparent increase in the oxygen consumption of slices of brain tissue prepared from these animals, although that of kidney and liver



was increased 28 per cent and 52 per cent respectively. On the other hand, Rossiter (92) was able to obtain a 43 per cent stimulation of metabolism in the presence of glucose and a 14 per cent stimulation with pyruvate when a brei of rat brain was used. If the diet of the animals did not contain extra vitamin B<sub>1</sub>, these effects were minimized. A finely ground brain dispersion did not show any differences under the influence of thyroid. Macleod & Reiss (93) found no diminished oxygen consumption by rat brain slices following hypophysectomy, although treatment of the animal for a week with thyrotropic hormone increased the brain metabolism. A similar enhancement was shown by normal brain, although to a lesser degree. Liver slices exhibited a decreased metabolism following removal of the pituitary and were restored by thyrotropic hormone administered *in vivo*.

Belasco & Murlin found a somewhat comparable fall in B.M.R. and in  $Q_{O_2}$  of thyroid tissue of young rats after four months of age (94). The injection of thyroxine into the animals caused a decrease in thyroid  $Q_{O_2}$  of rather inconsistent magnitude, in contrast to thyrotropic hormone which produced a gradually increasing stimulation after four months. The corresponding changes in metabolic response of liver and kidney cortex slices have also been studied (95).

An increase of 70 per cent in the oxygen consumption of the thyroid of the guinea pig was found one day after the first administration of thyrotropic hormone (96). This level was maintained for two more days and then fell (with continued injections) to about 20 per cent above the original level. These authors considered that iodide exerted a direct inhibitory influence on the thyroid gland, since potassium iodide given along with the thyrotropic hormone limited the rise in thyroid metabolism to 20 per cent throughout the entire period. Stephens & Belasco (97) following up the histological observation that the thyroid of the guinea pig went into a resting, inactive state during chronic undernutrition, reported a decrease of 22 to 44 per cent in the metabolic rate of the gland, depending on the method of calculation.

Interest in the profound metabolic changes in the whole animal following removal of the adrenal cortices has stimulated investigation of tissues from these animals. Tipton (98) found a 26 per cent decrease in oxygen consumption of sliced kidney cortex, and 32 per cent decrease with liver slices. The usual marked stimulating effect



of pyruvate on liver metabolism was greatly diminished, and also, to a lesser extent, that of succinate. A high salt intake which improves the general condition of adrenalectomized animals caused a considerable return towards normal in the  $Q_{O_2}$  of liver. Working with kidney cortex, Russell & Wilhelmi (99) reported a marked reduction in oxygen consumption in the absence of substrate, and less than the normal stimulation with *dl*-alanine, *L*-glutamic, pyruvic,  $\alpha$ -ketoglutaric, and succinic acids. Ammonia production at the expense of the two amino acids was also reduced. The injection into the animals of cortical extract or of desoxycorticosterone returned the tissue functions to normal rates or even higher.

The injection of estrone into rats about doubled both the oxygen consumption and anaerobic glycolysis of excised uterine tissue (100). No effect was found from the addition *in vitro* of either estrone or estriol. The older observations of a normal rate of metabolism per unit weight in muscles atrophied following denervation (Knowlton & Hines) contrast with the increased  $Q_{O_2}$  of skeletal muscle atrophied because of experimental vitamin-E deficiency (101). The tentative explanation was made that  $\alpha$ -tocopherol might exert some sort of regulatory influence on enzymatic processes concerned with cellular oxidation.

*Conditions in vitro.*—Although the previous condition of the animal has considerable influence on the metabolism of tissues excised from that animal, it should be apparent that the changes subsequently produced in the tissues or their environment are of even greater importance for optimal survival. Many reports have included a study of experimental conditions restricted to a particular point of interest, but there has grown out of this work no general agreement concerning preparation of tissue or medium to be used. Some laboratories use tissue minced in the Latapie machine or homogenized according to the method of Potter & Elvehjem and consider their results as being directly comparable with those on so-called "intact" tissue, as well as representing processes taking place *in vivo*. Interpretation of such experiments must be tempered by a consideration of the drastic alterations in cellular function following disruption of cellular organization. A second consideration is the medium used. In spite of such studies as that of Kleinzeller (102), there is wide disagreement regarding optimal solutions for *brei* experiments. Among the contributing factors are the incomplete information about the loss of coenzymes and other



factors necessary to the proper functioning of the various enzymes present in tissue brei, and the uncertain validity of oxygen consumption as the criterion of optimal function. Too often, an increased metabolic rate resulting from the addition of some substance is interpreted as an "improvement." Furthermore, if the principal interest in tissue mince experiments concerns intracellular processes, one wonders why sodium rather than potassium is so often used as the main cation present in the medium.

Serum has long been used as a medium for tissue slices to provide a source of colloid osmotic pressure but technical difficulties have largely limited its wider use. The use of "neutralized" serum (103, 104, 105), in which bicarbonate has been decomposed by treatment with hydrochloric acid, eliminates the complication of carbon dioxide buffering. Serum is however, not a "basal" medium. Lactic acid and other intermediaries of red cell metabolism may accumulate during its preparation; this complication may be dealt with by dialysis and replacement of electrolytes. The contribution of its phospholipid and protein content to respiration also requires analysis. Furthermore, it is more physiological to dilute serum to a protein content similar to the lymph in which the tissues are bathed (106). All these factors will require further study before the best use can be made of serum as a medium for studies of metabolism *in vitro*.

*Respiration of various tissues.*—Macleod (107) found that human spermatozoa studied in Ringer-phosphate-glucose solution exhibited a high aerobic glycolysis, about 80 to 90 per cent of the anaerobic glycolysis, with very low uptake of oxygen. In fact, motility in the presence of glucose fell off much more rapidly in oxygen than in nitrogen, and aerobic glycolysis was not maintained as well as anaerobic. Ross, Miller & Kurzrok (108) reported no quantitative differences in metabolism of human spermatozoa divided into three classes according to probable fertility. These workers also found very low oxygen consumption.

Bovine spermatozoa have an appreciable uptake of oxygen, which is inhibited together with motility by 0.01 and 0.1 mg. gramicidin per cc. of suspension after an incubation period (109). The uptake of oxygen by seminal fluid, also noted by Macleod (107), was studied in detail by Winchester & McKenzie, using semen of the boar (110). They found that cell-free seminal plasma consumed 5 to 22 per cent of the oxygen used by the whole semen but this



could be eliminated by treatment with mercuric chloride or merthiolate, or by passing it through a porcelain filter. Although bull spermatozoa had an oxygen consumption about twenty times that of the human, at least part of their energy requirements was met preferentially by glycolysis (111). When sugar was not available for glycolysis, intracellular phospholipids were oxidized in order to maintain motility. That some such mechanism may exist to a slight degree in human sperm is suggested by the fact that motility in a nonnutrient medium could be revived better after exposure to low oxygen tensions (2 to 5 per cent) than after either anaerobiosis or exposure to pure oxygen (112).

Warren has amplified and extended his earlier studies on the metabolic characteristics of rabbit bone marrow involving the use of neutralized serum as medium (113). He drew the general conclusions that the typical erythroid cell probably would have no aerobic and only a low anaerobic glycolysis. On the other hand, the myeloid cell would show a high aerobic, and a very high anaerobic glycolysis. The oxygen consumption would be only slightly lower in the myeloid than in the erythroid type, while the characteristics of the average normal marrow would lie in between these two extremes. The cytochrome oxidase activity of rat bone marrow was markedly decreased when the animals were made copper-deficient, and showed an immediate increase after initiation of copper feeding (114). Hematopoietic stimuli, such as hemorrhage, low oxygen tension, or cobalt feeding, caused a rapid increase in the cytochrome oxidase activity of the marrow, and Schultze concluded that a close relation existed between oxidase activity of marrow and its ability to form hemoglobin and erythrocytes. It is interesting that, although lowered oxygen tension *in vitro* produced only the usual effects of partial anaerobiosis (decreasing oxygen consumption plus increasing glycolysis), the erythropoiesis of decreased oxygen *in vivo* caused a higher rate of respiration in proportion to glycolysis (115).

Brain *in situ* has been found not to oxidize appreciable amounts of lactic acid (116) or of the ketone bodies (117). Working with chopped white and grey matter from various portions of the brain of adult rats, Himwich *et al.* have found the  $Q_{O_2}$  for brain stem 20 per cent lower than for cortex (118). Cerebellum was 45 per cent lower than cortex and medulla 50 per cent. The chopped entire brain of infant animals consumed only two thirds as much oxygen



as did the adult medulla. The resistance of the infant to conditions involving lack of oxygen may be explained as due to the very low oxygen requirement as well as to a source of anaerobic energy which is not available to adult brain (119, 120, 121). The potentialities of the dehydrogenase and cytochrome systems have been found to be less in infant than in adult brain (122). In addition, the enzyme systems are probably working much closer to their maximum in the infant (123), and anaerobic mechanisms may be relied upon more often to furnish necessary energy.

In a detailed comparison of the  $Q_{O_2}$ 's of various portions of the infant and adult dog brain, Himwich & Fazekas (124) point out that, in the latter, the caudate nucleus and the cerebral cortex have the highest metabolic rates whereas the medulla and mid-brain are highest in the week-old puppy. The change in  $Q_{O_2}$  of the other portions with adulthood was in accordance with the concept of early dominance by the lower centers being superseded later by the higher centers. Essential corroboration of these changes has been given in a preliminary report by Tyler & van Harreveld (125).

Jejunal mucous membrane studied in Ringer-bicarbonate-glucose solution showed a high rate of respiration but no Pasteur effect, since both aerobic and anaerobic glycolysis were the same, numerically equal to the  $Q_{O_2}$  (126). In serum, the  $Q_{O_2}$  was the same, but both glycolyses were higher. Rosenthal *et al.* found (127) that the velocity of lactate production from added glucose by bovine articular cartilage remained proportional to the cell count which decreased 75 per cent from infancy to old age. Nonnutrient oxygen consumption fell off more rapidly than the cell count.

Hook & Barron have reported the brown adipose tissue ("hibernating gland") of the ground squirrel to be as metabolically active on a fat-free basis as kidney cortex (128). Furthermore, at hibernation temperature (8°C.), the oxygen consumption of the kidney slices fell to 15 per cent of that at 38°, whereas the brown adipose tissue was 36 per cent as active at the low temperature as at the higher. The gland can thus be considered very active during hibernation as well as during periods of activity.

*Effect of various poisons.*—Stannard (129) has extended his earlier studies on the differentiation of resting from activity metabolism in frog muscle to several other inhibitors besides the azide and cyanide used previously, and Stern & Fisher have added several narcotics (130). These results further substantiate the con-



cept that the cytochrome-cytochrome oxidase system functions only after stimulation, a thesis also supported by Korr's experimental findings on mammalian tissues "physiologically" stimulated (131): salivary glands by acetylcholine and epinephrine, pancreas by secretin, and myometrium by oxytocin. Even though the Warburg-Keilin system is potentially active in a resting tissue, it does not participate in respiration until stimulation somehow effects a release. However, Krahle *et al.* (132) question this interpretation, and they suggest that these results may be due to the ability of the inhibitor-cytochrome complex to transfer hydrogen at an oxidation-reduction potential lower than that of the corresponding portion of the cytochrome system itself. This would involve a reshuffling of the hydrogen carrying mediators which undoubtedly would have quantitative repercussions.

Bernheim & Bernheim have presented a study of the inhibitory effects of triiodobenzoate and of monoiodoacetate on the oxidation of glucose, lactate, and pyruvate by washed whole rat brain (133). The benzoate was found to be only a third as active as the acetate. The same authors have found that the oxidation of glucose, mannose, maltose, and fructose can be inhibited by iodoacetate, triiodobenzoate, and fluoride (134). Glucose and mannose inhibited the oxidation of maltose and fructose.

Baernstein & Grand (135) pointed out that studies of the toxic effect of lead *in vitro* had neglected the marked fall in pH which occurred when lead acetate was added to the usual Ringer-phosphate medium, due to extensive precipitation of lead phosphate. They found only a doubtful effect of the solution-suspension with pH elevated to 7.4, but considered the lead inactive in the resulting medium as well as in a citrate solution although the latter gave a 10 per cent decrease in  $Q_{O_2}$ . Since, in accord with the study by Stearns *et al.* (136), the low pH of the lead-Ringer-phosphate solution was found to be 90 per cent reversible after thirty minutes, this procedure was also tried. No net effect was found with 0.001 per cent lead, but a 14 per cent depression with 0.002 per cent.

Methylene blue in the high concentration of 0.5 mg. per cc. has been found to cause a 48 per cent stimulation in oxygen consumption of rat liver slices in inactivated human serum (137). It is also able to restore respiration inhibited by chloral hydrate, but not by sodium barbital, this fact indicating a differential action of the two drugs. The prolonged administration of morphine to



rats increased the  $Q_{O_2}$  obtained from minced skeletal muscle but not that of several other tissues studied (138, 139). The *in vitro* addition of morphine to minced muscle similarly caused a greater oxygen consumption and increased the oxidation of pyruvate (140).

*Metabolism of tissue derivatives.*—The series of reactions ("citric acid cycle") proposed by Krebs as the mechanism of oxidation of pyruvate has received considerable attention. Smyth (141) concluded that the oxidation of pyruvate by minced sheep heart proceeded through the citric cycle, since many of the test reactions applied to the pigeon mince were satisfied by this tissue. Krebs *et al.* (142) noted the formation of various intermediate compounds from oxalacetate by minced sheep testis, heart, and brain, and guinea pig kidney, as well as pigeon breast muscle. Because of variabilities and conflicting results with sheep testis and brain, the quantitative importance of the citric cycle is difficult to assay in these tissues. Evans (143) presented evidence casting considerable doubt on the existence of the cycle in minced pigeon liver: the oxidation of added pyruvate was incomplete; malonate inhibition of succinic dehydrogenase did not interfere with pyruvate utilization as in muscle. The bulk of the pyruvate disappearing in liver suspensions could be accounted for on the basis of formation of  $\alpha$ -ketoglutaric and acetoacetic acids. By the use of bicarbonate containing radioactive carbon, Evans & Slotin (144) were able to show the incorporation of carbon dioxide into the  $\alpha$ -ketoglutarate formed from pyruvate by minced liver. Krebs & Eggleston (145) independently found that the utilization of pyruvate and the formation of intermediates such as citrate,  $\alpha$ -ketoglutarate, succinate, and fumarate were increased by the presence of bicarbonate and carbon dioxide. They suggested a carbon dioxide carboxylation of pyruvate to form oxalacetate, which then would combine with a second molecule of pyruvate to form citrate, in turn oxidized to  $\alpha$ -ketoglutarate. Thiamin was shown to be involved in the general reaction. Although this work was at first interpreted as support for the citric cycle theory in minced liver, Evans has since reported (146) that the distribution of the radioactive carbon in the synthesized ketoglutarate was at variance with that to be expected from the theory.

Colowick, Kalckar & Cori (147) have continued work on the "coupling" of glucose phosphorylation with oxidative processes



in extracts of heart, kidney, liver, and brain. In general, the oxidation of glucose (also through a phosphorylative pathway) and, in some cases, of glutamic, pyruvic, or succinic acids can be used for the extensive transformation of glucose into fructose diphosphate. The esterification of glucose or of hexose monophosphate by dialyzed pigeon brain preparations in the presence of adenylic acid has been found to be connected with the oxidation of pyruvate catalyzed by the four carbon dicarboxylics (148).

Lipmann has elaborated the concept of classifying organic phosphate compounds according to the potential energy of the phosphate bond (149). The larger group, including all simple esters of phosphoric acid with an alcoholic hydroxyl shows a lower range of fall in free energy when the ester linkage is split (2,000 to 4,000 calories), as contrasted with changes calculated to be about 9,000 to 11,000 calories for the "energy-rich" group. The latter comprises such phosphate bonds as P-O-P (adenyl pyrophosphate), N-P (creatine-phosphate), carboxyl-P (phosphoglyceryl-phosphate), and enol-P (phosphoenolpyruvate). Since there is a continual turnover of phosphorus from the low-energy ester form to the high-energy form and vice versa, there is maintained a reservoir of energy readily available for such processes as muscular contraction, resynthesis of glycogen, bone formation, etc. The turnover of labile organic phosphate in heart muscle slices appeared to be concerned more in the overall metabolic rate of the tissue than in oxidation of any specific type of foodstuff (150).

Several studies have appeared on reactions involving cytochrome-*c*. Altschul *et al.* have found the reaction between reduced cytochrome-*c* and hydrogen peroxide to be catalyzed by a new iron-containing enzyme called cytochrome-*c* peroxidase, which was isolated from baker's yeast (151). Other workers at the same laboratory have reported (152) the isolation of cytochrome-*c* reductase, a new flavoprotein which catalyzes the reaction between reduced triphosphopyridine nucleotide and oxidized cytochrome-*c*. This last reaction completed the oxidation-reduction chain from hexose monophosphate to cytochrome-*c*. Cytochrome-*c* has been shown by Lockhart & Potter to be part of the hydrogen transport mechanism from reduced coenzyme I to oxygen (153). Since Potter has eliminated cytochrome-*b* as an essential step in the reduction of cytochrome-*c* (154), there is a strong support for the direct reduc-



tion of cytochrome-*c* by a flavoprotein which, in turn, would react with reduced coenzyme I (155).

Graubard has reported inhibition of the oxygen uptake of whole rat and rabbit uteri in a similar manner to the inhibition of cytochrome oxidase preparations from the same tissues (156). The author considered that the oxidase could be directly responsible for the overall respiration of the tissue, but also pointed out that there might be other reactions so linked as to be equally determinant.

Several reviews, which have appeared on various phases of energy-yielding mechanisms, are cited briefly here because of space limitations. The subjects are as follows: intermediary metabolites and respiratory catalysis, by Elliott (157); nature of energetic coupling in biological syntheses, by Kalckar (158); mechanism of hydrogen transport in animal tissues, by Potter (159); changing concepts of chemistry of muscular contraction, by Sacks (160); blood sugar: its origin, regulation and utilization, by Soskin (161); and fat metabolism in diabetes mellitus, by Stadie (162).

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DEPARTMENTS OF PHYSIOLOGY AND MEDICINE  
CORNELL UNIVERSITY MEDICAL COLLEGE  
AND THE NEW YORK HOSPITAL  
NEW YORK CITY, NEW YORK  
AND  
DEPARTMENT OF PHYSIOLOGY  
UNIVERSITY OF TENNESSEE COLLEGE OF MEDICINE  
MEMPHIS, TENNESSEE



## THE PHYSIOLOGY OF THE SKIN

BY PERRY C. BAIRD, JR., AND WALTER F. LEVER

*Massachusetts General Hospital, Boston, Massachusetts*

AND

TOM D. SPIES

*Department of Internal Medicine,  
University of Cincinnati College of Medicine,  
Cincinnati General Hospital, Cincinnati, Ohio*

The physiology of the skin represents a field of science which is now more fully appreciated in its importance but which is only in its infancy as a problem for investigation. Nevertheless, the literature on the subject is too extensive to permit a discussion of all recent publications within limited space. This review has been restricted to a group of interesting and important contributions which have appeared in the literature concerning cutaneous physiology during the last two years.

*Perception of pressure, pain, and itching.*—It is generally agreed that the sensory nerves of the skin mediate four different qualities of sensation, namely, pressure, warmth, cold, and pain, and that the first three sensations arise in response to stimulation of specific receptors for each sensation, while pain is mediated through free nerve endings in the skin. These free nerve endings have been studied in recent years with reference to their anatomical, physiological, and biochemical properties and important conclusions were possible, although it will be evident from the following discussion that general agreement has not been obtained by the various investigators.

Rothman (1) in discussing the physiology of pain and itching agrees in the essential points with Head (2), Lewis & Pochin (3), and Erlanger & Gasser (4). Rothman regards the sensory nerves with free nerve endings as specific pain fibers. He distinguishes, in accord with Head, between two types of pain perception, sharply localized epicritic pain ("first pain"), and the diffuse protopathic pain ("second pain"). Rothman further confirms Erlanger & Gasser's observation, that the epicritic pain is a function of thicker, fast conducting, myelinated fibers, which Erlanger & Gasser called A and B fibers, while the protopathic pain is a function of thinner, slow conducting, unmyelinated fibers, C. fibers. Itching is regarded as a protopathic pain sensation and "whether tickling, itching or



protopathic pain sensation is felt, depends only on the frequency of impulses in the slow conducting fibers." Scratching in response to itching is, according to Rothman, a means of suppressing a protopathic pain, by the more tolerable epicritic pain. The "nocifensor system" of nerves to which Lewis (5) has attributed the hyperalgesia around injured areas is regarded as identical with the protopathic system.

In contrast to Rothman, Achelis (6) doubts the specificity of the sensory nerves with free nerve endings as pain nerves. He reverts to the theory of Goldscheider (7) that these nerves may convey, besides pain and itching, a general tactile sensation and, in order that they may convey pain, a "neuron threshold" must be overcome. This general tactile sensation exists in addition to a specific tactile sensation perceived in the specific touch receptors, which are in close anatomical relation to the hair follicles. Achelis cites, as proof of the existence of touch sensations outside the specific touch receptors, firstly, the experiments carried out by Becker & Fröhle (8) in his institute in Heidelberg. They "proved that tactile sensations can be elicited between touch receptors and that this sensation is not produced by simultaneous stimulation of the touch receptors." Secondly, he maintained that painfree touch sensations can be elicited on the cornea, glans, and clitoris, areas which do not have any specific touch receptors, by dull stimuli with smooth surface, for instance by slightly touching the cornea with a moistened finger. Thirdly, the electrophysiological studies of Zotterman (9) have shown that B and C waves, originating in the thinner (B and C) fibers of the sensory nerves, and regarded by Zotterman, as well as many others, as the axon potentials of pain, occur also in response to touch and very light stroking. Achelis, therefore, concludes that a "fiber-physiological specificity" does not exist, that the same fibers may conduct touch, pain, and itching. According to him, the type of sensation felt depends as well on the type of stimulus as on the fiber. A small surface stimulus of high intensity is optimal for pain production. He acknowledges, however, that the thin, slow conducting fibers (C fibers) are optimal for pain perception.

Wollard, Weddell & Harpman (10) examined the anatomical basis of cutaneous pain perception. They used the technique evolved by Clark *et al.* (11) for staining nerves *in vivo*, by injecting



small volumes of methylene blue solution into local blood vessels. By this method, the existence of widely branching nerve plexus in the cutis was demonstrated. According to the authors, the epicritic pain, which they call superficial pain, is due to stimulation of superficial nerve terminals, the protopathic pain or deep pain is experienced when several fibers of the nerve plexus in question are stimulated. The authors believe that the greater intensity and diffuse character of deep pain can be explained on the basis of spatial summation. They suggest that the delay in onset and the persistence after stimulation of deep pain are related to the number of nerve fibers stimulated in a single nerve bundle. The authors conclude that both varieties of cutaneous pain, the epicritic, as well as the protopathic pain, are subserved by the same nerve apparatus, and that there is no need to assume the existence of two systems of fibers in cutaneous nerves.

Rein (12) discussed the problem of pain production from a chemical angle and maintains that formation of a *Schmerzstoff* (pain substance), which is a decomposition product of injured cells, is necessary for pain and that it is the action of the *Schmerzstoff* on the nerve endings, which produces pain. Rein cites, as proof of his contention that pain is produced by chemical action, the fact that the van't Hoff law is applicable. This law maintains that a rise in temperature of 10°C. doubles the velocity of reaction for chemical processes. Rein states that hyperemia is not the cause of pain, but produced by the same stimulus. He regards the hyperemia as a defense mechanism, which may be sufficient to prevent the accumulation of the *Schmerzstoff*.

Rein does not profess to know the chemical composition of the *Schmerzstoff*. He thinks a great variety of chemicals may act as mediators of pain, among them histamine. Rosenthal & Minard (13) cite experiments to prove that painful electrical stimulation of the skin or cornea liberates histamine and that the amount of histamine is directly proportional to the degree of stimulation. They assume, therefore, that histamine may be the chemical mediator of pain, "much as acetyl choline and sympathin are the mediators in the case of the autonomic nervous system."

Interesting observations on the threshold of cutaneous pain were reported by Wilder and by Hardy *et al.* Wilder (14) found that while the threshold for pain varies among individuals, it is gener-



ally higher for men than for women. In patients with functional diseases the pain threshold is significantly lower than in patients with organic complaints.

Hardy, Wolff & Goodell (15), with the aid of a new quantitative method of measuring the threshold of pain evoked by thermal radiation, found that intense pain produced in any part of the body raised the pain threshold in the skin of other parts of the body as much as 35 per cent. Tight bandaging of the head, raised the pain threshold of the forehead 5 to 15 per cent; a similar rise could be effected by letting the patient grip a bar tightly. Administration of 1.8 grams of acetylsalicylic acid was followed by a rise in the pain threshold amounting to 35 per cent.

It has long been a controversial issue whether there exists a separate vibratory sense or whether vibratory sensations are mediated by the same mechanism as pressure sensations. In spite of refinements in the methods for measuring sensory functions during recent years, the controversy still exists.

Cummings (16) presents experiments which, in his opinion, indicate the existence of a separate vibratory sense. He measured alterations in pressure and vibratory thresholds following local (electroendosmotic) cocaine anesthesia. Whereas tactual sensitivity was abolished in the test area, there was only a slight elevation of vibratory thresholds. Considering the possibility that conduction to other tissues might be responsible for the apparently preserved vibratory sensibility, Cummings anesthetized a larger area (9 sq. cm. as compared with the previous 4 sq. cm.) and again measured the vibratory loss. Since no further diminution occurred under these conditions, Cummings concluded that the superficial touch receptors have only a slight role to play in vibratory mediation.

Weitz (17) repeated these experiments. By testing the vibratory sense with a fine vibratory needle he found the anesthetized skin as insensitive locally to vibration as to pressure. These vibrations, although produced within an anesthetized area, however, were clearly felt in the surrounding not anesthetized skin, due to their mechanical transmission over large areas. Because it was in his opinion merely this transmitted vibration which Cummings had been measuring, he believed that Cummings' argument for an independent vibratory sense was void.

As further proof for the identity of pressure and vibratory



sense, Weitz (18) presents his experiments in regard to the effect of warming and cooling of the skin on the threshold of vibratory and pressure sensation. Both thresholds fall with increasing skin temperatures and rise with decreasing skin temperatures in identical curves.

Geldard (19) shares Weitz's view. He traced all pressure-sensitive spots on a small area of skin and found the threshold of vibratory sensation to average 13.6 micra in these spots, whereas in the pressure insensitive regions, between the pressure sensitive spots, the vibratory threshold was over eight times as high.

In contrast to Geldard, Békésy (20) found that the points most sensitive to pressure and those most sensitive to vibration were, as a rule 0.5 mm. apart. He believed that those two sensations originate in different neural terminations. He located the nerve endings conveying vibration in the hair papillae and those conveying pressure around the hair follicles at the level of the sebaceous glands. The distance of 0.5 mm. on the surface of the skin between the points responding to pressure and to vibration was explained by the slant of the hair follicle.

*Pharmacodynamic action of various drugs on the skin.*—Alexander, Elliot & Kirchner (21) investigated the mode of action of a number of wheal producing drugs on the capillaries of the skin. They attempted to establish whether wheal formation following the iontophoretic introduction of these drugs into the skin was by direct action on the capillary walls or by indirect action through the release of H-substance. The presence of capacity for repeated wheal production at the same site excluded the intermediary action of H-substance, since Grant, Pearson & Comeau (22) had shown that once the H-substance was released an interval of some forty-eight hours had to elapse before H-substance could be released again. It was found that histamine always produced wheals when reapplied, which fact permitted the conclusion that it acted directly on the capillary walls; pilocarpine and physostigmine did not produce wheals when reapplied until forty-eight hours had elapsed, so that it could be assumed that they formed wheals by release of H-substance from the skin cells. Repeated application of codeine, morphine, and atropine produced smaller wheals than did their first application, which indicated that they acted on the capillary walls, both directly and through release of H-substance. The fact that different types of wheals were produced by histamine and H-



substance was regarded by the authors as a proof that histamine and H-substance were not identical. Of clinical interest is the observation of the authors that the wheals of urticaria do not recur at the same site within forty-eight hours. They behave, in this respect, like the wheals caused by pilocarpine and physostigmine, and not like those caused by histamine. The authors concluded, therefore, that H-substance and not histamine must be the urticariogenic factor in the skin.

Rothman & Coon (23) investigated whether or not acetylcholine could be demonstrated in mechanically injured skin and in the skin of patients with inflammatory dermatoses. The possibility that acetylcholine was liberated in injured or inflamed skin was considered, because mechanical injury, as well as inflammation of the skin, produces a general stimulation of the parasympathetic nervous system and acetylcholine is the chemical mediator of the parasympathetic system. Acetylcholine was assumed to be present in the tested material, if it produced a depression of the blood pressure of the cat, or a contraction of the physostigminized leech muscle, as acetylcholine does. No acetylcholine effect could be demonstrated in the skin or outflowing venous blood after injury to the skin. Yet, in the tissue fluid of wheals produced by histamine, the presence of acetylcholine could be demonstrated in four out of nine cases. The dermal tissue fluid was examined in six patients with inflammatory dermatoses and the presence of acetylcholine could be demonstrated in five. It is of interest that the fluid from vesicles in one case of dermatitis herpetiformis, and one of pemphigus, caused contraction of physostigminized leech muscle. Although the authors present experiments supporting their assumption that the substance which affected the blood pressure of the cat and physostigminized leech muscle actually was acetylcholine, they realize that the evidence is not conclusive. Furthermore, they point out that acetylcholine could not be demonstrated constantly in the cases tested. The authors, therefore, regard their report as preliminary and suggest further experiments.

Rothman & Coon (24, 25) further studied the action of intradermal injections of acetylcholine on the skin. They were able to confirm by their experiments Brücke's (26) observation that acetylcholine has two different pharmacological effects, a muscarine-like action and a nicotine-like action. Intradermal administration of acetylcholine produces three reactions in and around the area of



injection: firstly, goose flesh, due to its action on the pilomotor muscles; secondly, sweating; and thirdly, vasoconstriction. Investigation of the mechanism of these three responses led the authors to the following conclusions. (i) The pilomotor action of acetylcholine occurs by virtue of its nicotine-like action. Acetylcholine as well as other drugs with nicotine-like action as, for instance, choline, choline esters, and alpha-lobeline, provoke pilomotion through an axon reflex in the ramifications of the peripheral sympathetic axon within the skin. (ii) The sweating at and around the site of injection is provoked in two different ways: first, by a direct action on the sweat gland, a muscarine-like effect; and secondly, by an indirect action through an axon reflex mechanism, a nicotine-like effect. The two axon reflexes of acetylcholine producing pilomotion and sweating resembled each other in all the points studied with two important exceptions. Firstly, atropine abolished the sweat but not the goose flesh response; secondly, ergotamine abolished the pilomotor but not the sweat response. This difference is explained by the fact that while the effector ends of the fibers mediating the pilomotor reflex are adrenergic, those of the sweat response are cholinergic. The pilomotor and sudomotor reactions to acetylcholine, therefore, are regarded as two independent phenomena. (iii) The vasoconstriction which appeared at and around the point of acetylcholine injection paralleled the piloerection in the rate of onset, duration, and drugs which would produce or abolish it. No way was discovered to obtain vasoconstriction without associated goose flesh. All three, the pilomotor, the sudomotor, and the vasomotor responses after intradermal injection of 0.1 cc. of acetylcholine could be observed over an area greater than 5 cm. in diameter, an indication of the wide extension of the ramifications of the stimulated axons. The authors ask themselves whether external cutaneous stimuli, such as cold stimuli eliciting pilomotor action or heat stimuli eliciting sweat secretion, stimulate the same nerve endings as do acetylcholine and nicotine, and whether these physiologic stimuli also act through an axon reflex mechanism. The opinion is expressed that the primary confined response to heat or cold is evoked by liberation of acetylcholine and is based on an axon reflex mechanism, whereas the subsequent general response is due to a spinal reflex mechanism.

The dermovascular action of subcutaneous injections of estrogen was investigated by Reynolds (27). He studied its effect on the

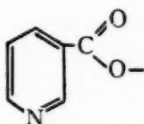


blood vessels of the ear in ovariectomized rabbits and on the finger volume in human beings. In the rabbit's ear, it was found that following the administration of estrogen numerous cutaneous capillary loops opened which had been closed before, so that the ground color of the ear became pinkish. The skin temperature did not change materially. The finger volume of human males increased an average of 4.6 per cent, a considerable increase if one considers that it was solely due to the dilatation of blood vessels. No increase in the temperature of the finger was observed. The absence of temperature increase indicates that the vasodilatation was effected without a significant alteration in the rate of blood flow. As the blood flow is regulated by the lumen of the arterioles, it follows that the vascular dilatation after administration of estrogen occurs beyond the smallest arterioles, namely, in the capillaries and venules. The change in the finger volume of women with menopausal disturbances did not always follow the pattern observed in males; instead of a gradual steady increase in the finger volume, a much faster increase could be observed frequently with an increase in temperature, so the conclusion was drawn that arteriolar dilatation may occur in such patients.

Bean & Spies (28) discuss the dermovascular action of nicotinic acid and of related pyridine and pyrazine compounds. Measurements in a constant temperature room proved that the vasodilatation following oral or parenteral administration of nicotinic acid was accompanied by a rise in the temperature of the skin. The earliest and most striking temperature changes were in face and neck. In some cases, a rise in temperature occurred over the entire body surface, but often the arms and legs escaped the reaction; in the legs the temperature actually dropped in some instances. It was found that, if epinephrine was injected beforehand, the dermovascular reaction was decreased. The antagonism which exists between epinephrine and nicotinic acid, as far as their action on the cutaneous vessels is concerned, led the authors to the conclusion that nicotinic acid acts upon the arterioles of the skin. Since histamine and nicotinic acid are very similar in their action on the cutaneous vessels, the authors suggest that nicotinic acid may function through liberation of histamine in the tissues. Upon investigating which of the pyridine compounds, in addition to nicotinic acid, produced vasodilatation in the skin, it was found that only those of the structure shown in Formula I demonstrated this



property. Substitution or addition of radicals except at the unsaturated oxygen atom abolished the response. Accordingly, vasodilatation followed the administration of the sodium, ammonium, ethyl, and monoethanolamine salts of nicotinic acid but did not



FORMULA I

result from quinolinic acid, nicotinic acid amide, pyrazine, pyridine, sodium sulfapyridine, and pyridoxin. The beneficial effect on pellagra and the vascular reaction are not necessarily caused by the same molecule, because some of the effective antipellagric compounds do not produce vasodilatation. Pyrazine monocarboxylic acid produced vasodilatation, but of less degree and less regularly than nicotinic acid.

Unpublished observations by these same investigators (29) have revealed that bismuth, ferrous quinine, and ethyl glucamionium nicotinate all produce vasodilatation of the skin. Nicotinuric acid was inactive under the same circumstances. It was not possible to prevent or reduce the vascular reaction to nicotinic acid by large parenteral and oral doses of "histaminase"<sup>1</sup> given for several days before administration of nicotinic acid.

*Heat regulation by the skin.*—Fundamental studies concerning the regulation of heat were carried out through the cooperation of Sheard, Roth, Horton, Williams, Kirklin, and Plummer (30, 31, 32, 33). Their experiments showed that in contrast to low environmental temperatures to which the human body adjusts itself by general constriction of the cutaneous blood vessels, the regulation of the dissipation of heat in the zone of comfortable environmental temperatures (23° to 30°C.) is accomplished chiefly by the tonus of the cutaneous blood vessels of the extremities. At a temperature of 18°C., the cutaneous blood vessels of head and trunk are already near to maximal dilatation, while those of the lower arms and legs still show considerable vasoconstriction, the legs more than the arms. Between 18°C. and 25°C. the regulation of the dissipation of

<sup>1</sup> The "histaminase" activity of this preparation *in vivo* has been questioned.



heat is chiefly accomplished through the skin of the hands and lower arms; at room temperatures between 25°C. and 30°C. the regulation takes place through various degrees of vasodilatation in the skin of the feet and lower legs.

With a gradual increase of the room temperature over 18° C., a rise occurs in the skin temperature of the hands and lower arms, until at 25° C. there is maximal dilatation of the cutaneous blood vessels and the skin temperature equals that of the head and trunk, namely, between 32° C. and 35° C. With increase of the environmental temperature above 25° C. the vasoconstriction in the feet gradually disappears and at an environmental temperature of 28 to 30° C., there is maximal vasodilatation also in the toes, and the temperature equals that of the rest of the body.

At atmospheric temperatures exceeding 31° to 32°C., maximal vasodilatation of peripheral blood vessels is maintained and the internal temperature of the body is kept approximately constant by changes in the secretion and subsequent evaporation of sweat. These experiments were carried out on healthy persons in basal metabolic state, since it had been found that ingestion of food caused an increase of skin temperatures of the fingers or toes respectively, dependent on the environmental temperature; furthermore, the supine position was maintained throughout the experiment, because lowering of the extremities effected a rise in their skin temperature. The relative humidity was regulated at 40 per cent.

It was, however, found that at an environmental temperature of 23° to 28°C., the relative humidity could be varied over a fairly wide range (35 to 75 per cent) without effect on the skin temperature of the body (29). This is, incidentally, in complete agreement with the results of Talbot (34) who, in 1931, had found that at environmental temperatures between 20° and 30°C. a variation of the humidity from 35 to 80 per cent did not influence skin temperatures.

The correlation between skin temperature and basal metabolism was investigated. The temperature readings were done on the toes at a room temperature of 25°C., because at this temperature the toes are the most sensitive indicator for changes in the dissipation of heat. Examination of a group of persons with normal and abnormal basal metabolic rates demonstrated a close relationship between the skin temperature of the great toe and the basal metabolic rate (31).

In patients with exophthalmic goiter the decrease in the basal



metabolic rate following the administration of Lugol's solution or following partial thyroidectomy closely corresponded to the decrease of the skin temperature of the great toe at an environmental temperature of 25°C. (32).

Examination of patients with Raynaud's disease and with thromboangiitis obliterans revealed a considerable delay in vasodilatation under rising environmental temperatures. While in normal individuals vasodilatation of the hands begins at 18° to 20°C. and of the feet at 25°C., no vasodilatation occurred in the hands of a patient with Raynaud's disease until the room temperature had reached 30°C.; this is in accordance with the clinical experience that patients with early Raynaud's disease are free from symptoms in warm climates where the temperature is constantly above 29°C. In a patient with early thromboangiitis obliterans a temperature of 29°C. was required to produce vasodilatation of the feet (33).

*Permeability and absorptivity of the skin.*—Eller & Wolff (35) investigated the permeability of the skin to various fats. The penetration was judged by the amount of fat seen in sections of the skin of rabbits following external application of various fats. The authors' article is supplied with excellent microphotographs which show clearly that fat permeates the skin along the hair shafts and sebaceous gland ducts. It was found that animal fats show the greatest depth of penetration, with vegetable fat next and mineral fats last. Liquid fats permeated the skin more rapidly than solid fats. Most of the fats showed optimum penetration between four and six hours after application. After six hours, the quantity of fat in the deeper tissues appeared to diminish. In the discussion following the presentation of the paper, Abromowitz stated that the absorption of fats by the skin was dependent among other things on their melting points.

Nelson, Greene & Wells (36) investigated the influence of the solvent and of esterification on the degree of percutaneous absorption of testosterone and compared with effectiveness of percutaneous with subcutaneous administration. Effectiveness was judged by the increase in weight of prostate and seminal vesicles obtained in castrated rats by the daily administration of 0.2 mg. of testosterone, or testosterone propionate, over a period of three weeks. The experiments established that both testosterone and testosterone propionate were better utilized when applied to the skin in alcoholic solution than when applied in ointment bases. Furthermore,



testosterone proved more effective than testosterone propionate on percutaneous application. The superiority of testosterone over testosterone propionate in regard to transepidermal penetration was also illustrated by the fact that percutaneous application of testosterone in alcohol was more effective than subcutaneous administration of testosterone in oil, while testosterone propionate was less efficient percutaneously in alcohol than subcutaneously in oil.

Behnke & Willmon (37) studied the rate of diffusion of gases through the skin under various environmental temperatures. Enclosing the whole body with the exception of the head in a bag filled with helium or nitrogen, they measured the amount absorbed through the skin by the quantity of helium or nitrogen exhaled through the lungs. When the temperature of the helium in the bag was 22°C., about 40 to 60 cc. of helium diffused through the skin per hour. Raising the temperature of the helium in the bag up to 28°C. did not lead to an increased cutaneous diffusion of helium, but when the helium was heated beyond 28°C., a linear increase in the diffusion of helium was found. At a temperature of 35°C., 170 cc. of helium diffused through the skin per hour, which constituted a threefold increase over the amount of helium absorbed at 28°C. The figures for the diffusion of nitrogen were approximately 50 per cent lower, but the rate of diffusion increased similarly with the rise of temperature. The abrupt linear augmentation of helium and nitrogen diffusion in the range of 28°C. and upward was assumed to be due chiefly to the increasing cutaneous blood flow at such temperatures. The authors base this assumption on the work of Hardy & Soderstrom (38) who had found that blood flow to the skin increased about threefold between 28°C. and 35°C., while below a temperature of 28°C. blood flow was minimal and constant.

*Photosensitivity of the skin.*—Miescher (39) discusses the effect of ultraviolet light on the skin. Radiation with ultraviolet rays causes hyperkeratosis and pigmentation. Both keratin and pigment are effective protectors against ultraviolet radiation, because they absorb ultraviolet rays to a great extent. The author points out the difference in light protection between white persons and negroes. In white persons, increasing tolerance of ultraviolet radiation is solely due to the hyperkeratosis and the protective effect of the pigment is negligible, because pigmentation occurs in white persons only in the basal layer and, except for very high doses, ul-



traviolet rays do not penetrate to such depth. In the negro, however, pigment extends throughout the rete Malpighii and damage to the skin from ultraviolet rays is, therefore, in the negro confined to the uppermost layers of the epidermis except in extremely high doses. Miescher, in investigating the extent to which keratin absorbs ultraviolet rays, found that an increase in thickness of the horny layer of only 8 to 9 micra reduced the effectiveness of short ultraviolet rays to one half. Two types of pigmentary reaction can be distinguished in the skin: first, the much more pronounced delayed pigmentation caused by ultraviolet light with a wave length below 3200 Å and, secondly, the instantaneous pigmentation by ultraviolet light with a wave length above 3200 Å. The first type of pigmentation is due to increased accumulation of pigment, the second type due to transformation of a paler form of pigment into a darker form by absorption of oxygen; warmth as well as long ultraviolet rays can mobilize the required oxygen.

Blum (40) investigated the mechanism through which sulfanilamide causes abnormal sensitivity to light. He emphasizes that the photosensitivity produced by sulfanilamide is due to sensitization of the epidermal cells to ultraviolet radiation and not due to any photodynamic action of the sulfanilamide. The sulfanilamide response differs from that obtained when the skin is subjected to photodynamic action in three ways. Firstly, the typical photodynamic response is a wheal surrounded by a red flare, whereas the sulfanilamide response is characterized by erythema without whealing. Secondly, the photodynamic response appears within a few minutes, the sulfanilamide response only after a latent period of an hour or more. Thirdly, the photodynamic response depends on the presence of oxygen, as proved by the fact that occlusion of the circulation with a sphygmomanometer cuff during the irradiation inhibits the photodynamic response but not the sulfanilamide response. A study of the wave lengths which produce the sulfanilamide response revealed that the active wave lengths could not be distinguished by tests with filters from those which produce normal erythema and pigmentation. These are not the wave lengths to which porphyrins photosensitize.

*Skin in pellagra and related deficiency syndromes.*—Studies of unilateral and asymmetrical skin lesions in pellagra by Bean, Vilter & Spies (41) revealed that any factor increasing skin metabolism (e.g., heat, infection) or producing chronic stasis of blood in the



skin (e.g., varicose veins, scars) favored the localization of skin lesions in the affected area. Following this observation, similar lesions were produced on one arm or leg of patients who were about to develop pellagrous erythema. An electric pad, weighted with sand bags sufficient to cause reactive hyperemia of the skin after ten minutes without heat, was then heated to 42° to 45°C. and kept in place for one hour, once or twice daily. This procedure, without effect on normal controls or pellagrins in spontaneous or induced remission, produced characteristic pellagrous erythema at the same time that spontaneous lesions occurred in symmetrical areas elsewhere in the skin.

Studies on vasomotor disturbances in individuals with vitamin-B complex deficiencies have been reported in detail by Periata & Blasco (42, 43) in pellagrins studied during the Spanish wars. They found marked reduction from the normal in skin temperature, especially in the extremities. Other vasomotor disorders were encountered. Similar disturbances in peripheral neuritis have been noted also by Wilkins & Kolb (44).

Unpublished observations by Moore, Spies & Cooper have shown that the pathological changes found in both the clinically affected and unaffected skin in pellagra consist primarily in a dyskeratosis and atrophy of the epidermis and inflammation of the dermis. Since the skin reacts favorably to treatment with nicotinic acid, it would seem that these changes are to a considerable extent reversible, and that they may represent a response on the part of the skin to a chemical irritant which is bound up with deficiency of the vitamin-B complex.



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MASSACHUSETTS GENERAL HOSPITAL  
BOSTON, MASSACHUSETTS

AND

DEPARTMENT OF INTERNAL MEDICINE  
UNIVERSITY OF CINCINNATI COLLEGE OF MEDICINE  
CINCINNATI GENERAL HOSPITAL, CINCINNATI, OHIO



## THE PERIPHERAL CIRCULATION

BY ALRICK B. HERTZMAN

*Department of Physiology,  
St. Louis University School of Medicine,  
St. Louis, Missouri*

The literature cited in this review includes American papers from the period September 1940 to and including August 1941, but recent irregularities in the availability of European journals and books suggested the desirability of including these as they became available, irrespective of date.<sup>1</sup>

### THE ARTERIAL CIRCULATION

*The arterial Windkessel.*—Quantitation of the reservoir function of the aorta and large arteries has often been attempted in the past in relation to the elastic properties of the arterial system and has been used in calculations of cardiac output, peripheral resistance, etc., particularly by the Munich school. In these calculations the length of the Windkessel is one of the quantities which must be determined. It is therefore of extreme interest that both theoretical analysis and experimental findings indicate that the effective length of the arterial *Windkessel* is a function of time during the pulse cycle (1), the *Windkessel* expanding during the systolic ejection in a manner analogous to the expansion of an explosion beginning at the center of a confined space, so that the effective *Windkessel* finally includes every artery which shows a pulse. The elasticity modulus is therefore also a time variable. Application of this concept is made to the propagation of the pressure and volume pulses, and to the calculation of cardiac outputs with new equations by means of the physical methods previously described by Broemser & Ranke and Wezler & Böger. Recent experience in the use of these methods in hypertension (2) supports a conservative position in the calculation of circulatory mechanics and cardiac output from pulse-wave data. The *Windkessel* function of the aorta is partly or wholly lost in the Valsalva experiment with corresponding effects on the propagation of the

<sup>1</sup> Papers dealing with methods (references 220 to 245), as well as monographs and reviews of the general topic (references 246-256), have been included in the bibliography although they are not discussed in the text.



pressure pulses (3). These changes occur to a less extent as aortic elasticity is decreased, as by calcification; hence the Valsalva experiment furnishes a method for estimating the latter.

The well-known decrease in extensibility of the aorta with age apparently can occur without obvious morphological changes (4). Aortic elasticity, as estimated by pulse velocity, decreases in aortic sclerosis approximately in proportion to the decrease in aortic movements, but the pulse velocity measurements are considered a more reliable indication than the roentgen kymographic findings of the severity of the sclerosis (5).

*Arterial systole.*—The active participation of the arteries in the propulsion of the blood by a sort of peristaltic wave obtains scant attention in current thinking, but it is supported by two lines of evidence: first, the recording of potentials from large arteries, which currents are timed with the propagation of the pulse but are not due to electrical artifacts created by the pulse wave (6); second, the propagation of a peristaltic wave which may be recorded mechanically (7). Neither type of observation seems wholly free from error but deserves repetition.

*The arterial pulse.*—The behaviour of the arterial system as a manometer of low frequency is used in the explanation of the anacrotic pulse of aortic stenosis (8). The rounded form of the wave is apparently due to the slower ejection which permits the arterial system to propagate a pulse more like the central pulse without interference from standing waves which result from the ejection. Studies with circulation models continue (9, 10). The propagation of the pressure wave in a rubber tube is so affected by the energy losses that a lengthening of the "crest time" results (9). A similar lengthening of the "crest time" of the finger volume pulses occurs in hypertension and arteriosclerosis (11) and during the reactive dilatation in the finger to local cold (12), probably because of changes in the resistance and elastic properties of the digital and pad arteries.

*Arterial blood flow.*—Opinion has generally held that relatively small changes in arterial diameter greatly affect flow (Poiseuille's law), but thermostromuhr records appear to deny this (13), the reduction in flow being much less than one might expect. In such experiments the artery is usually occluded with a clamp. If occlusion is over a sufficient length of artery by means of a cuff method, the correlation between flow and arterial diameter is good (14).



The limiting factor of the lumen of main arterial trunks in the maximal flow through a limb has been emphasized in the study of occlusive arterial disease (15).

Recovery of flow after the experimental occlusion of arteries is due to two mechanisms (16): first, an immediate recovery on deocclusion from the opening of pre-existing collaterals by an increased differential pressure; second, a later slow recovery possibly due to the formation of new collaterals. A rational basis for therapeutic venous occlusion is supplied in the increased arterial inflow which occurs during and not after the venous occlusion (17). Failure to observe an increase in flow in the human extremity after intermittent venous occlusion (18) may be due to the measurements of flow having been made after and not during the occlusion. The increase in flow is not due to a reactive hyperemia but rather to a rise in pressures in the affected vascular area during the occlusion, causing dilatation and lowered resistance.

The dynamic effects of a patent ductus arteriosus (19, 20) and of an arteriovenous fistula (21) have been carefully studied.

The normal circulation time, measured by the cyanide method, averaged twenty seconds for arm to sinus and thirty-eight seconds for foot to sinus (22), but when measured with the lobeline method (23) ranged from five to ten seconds. The time is greatly affected by the temperature of the extremities. Ether and paraldehyde gave comparable values for arm-to-lung time in normal subjects but not in patients in heart failure (24). Calcium gluconate time, but not ether time, is shortened in hyperthyroidism (25). Erratic values for cyanide time were obtained in refrigerated men (26). Atelectasis slows the flow through the collapsed lung, increasing the flow in the aerated lung (27).

*Arterial blood pressure.*—The correctness of auscultatory and of palpatory criteria has been objectively evaluated (28). Improvement in the Korotkow sounds occurs if the subject's arm is first raised and the venous system emptied before inflation of the cuff (29).

What is the normal range of blood pressure? The extensive work of Robinson (30) defining the normal range has been questioned on the basis of incorrect use of statistical methods (31). However, an independent statistical study (32) agreed with Robinson's conclusion that there is no physiological increase in the arterial blood pressure with age and set a value of 150 mm. Hg



as probably beyond the normal range. This value is higher than that set by Robinson. The blood pressures tend to be higher in the lateral or broad-built person in whom the incidence of hypertension is also greater (33); when the lateral build is combined with height, the hazard of hypertension is heightened (34).

The excitement factor in elevating resting blood pressures in hypertensive patients is illustrated in the higher values (as much as 70 mm. Hg) obtained by the physician compared with home determinations made by the patient or a relative (35). Comparison of student values taken by fellow students with University Health Service or Army determinations shows the same tendency in normal persons, emphasizing the possibility that the upper limit for normal values as set by the physician is probably too high.

*Experimental hypertension.*—The most active field in the study of the peripheral circulation is that of renal hypertension of the Goldblatt type. This subject is being reviewed elsewhere in this volume by Shannon.

Neurogenic hypertension produced by section of the moderator nerves can be permanent when Heyman's technique is carefully followed (36). Sympathectomy must be total to prevent it; this throws doubt on the therapeutic value of a partial sympathectomy, such as splanchnic section, in cases of hypertension in which nervous factors are the basis of the operation. The section of the moderator nerves still results in hypertension when only the sympathetic supply to the kidneys and adrenals remains; it is possible that the hypertension is then a renal type due to a renal ischemia from excessive vasoconstrictor activity. Intracisternal injection of kaolin has been a successful method of producing hypertension, but a recent failure with the method is reported by competent surgeons (37).

Attempts to produce hypertension by the long continued injection (two years) of epinephrine (38) and of tyramine (39) met with failure; it was concluded that neither substance was involved in pale hypertension in man. The pressor substances in shed blood are eliminated by the passage of the blood through the lung, liver, or spleen (40).

*Hypertension in man.*—Increase in the peripheral resistance is generally accepted as the major factor in clinical hypertension. The precapillary location of the resistance is indicated by the presence of normal capillary pressures in hypertensive patients (41). The changes in minute vessel pressure and the number of capillaries



opened (42) in the histamine flare vary greatly in different cases, probably in relation to the extent of sclerosis in the precapillary arterioles and arteries. Variations in the form of the volume pulse of the finger pad (11) in these patients may also be due to the effects of sclerosis as well as of resistance in the minute arteries. That the peripheral resistance may continue at a high level despite a fall in blood pressure after operation in hyperthyroid hypertensive patients is indicated by their hyperreactions to exercise and to the cold-pressor test (43); this argues for arteriolar disease.

The impression had developed from observations on peripheral blood flow that the increase in the peripheral resistance was generalized rather than selective with respect to certain vascular beds (e.g., splanchnic). But the resting blood flows in the forearm (44) and the relationship between forearm flow in reactive hyperemia and the blood pressure (45) seem to deny that the muscle vessels participate in an irreversible increase in resistance. However, these measurements, forceful as they are, are not necessarily indicators of the resistance changes in the individual arteries and arterioles, but they may instead record the size of the vascular bed per unit volume of muscle. The scatter of the data and the lability of the muscle circulation in training should make one very cautious in using muscle flow data as evidence for arterial narrowing.

The responses of the blood pressure to a standard exercise test are greatest in the high blood pressure groups of University students (46), as are also the reactions to the cold test. These exaggerated responses which seem to be due to an hyperreactive vasomotor system also correlate with the larger differences between basal and so-called resting blood pressures. They may have predictive value.

Space forbids a consideration of hormonal, nervous, and renal factors in the etiology of hypertension or of the effects of surgical treatment.

*Drug actions on blood pressure.*—The effectiveness of several hypotensive substances has been studied. Pancreatic extracts are active when injected intravenously (47) but not when administered orally. Prisol, a new dilator substance, acts on the minute arteries and arterioles (48); it is effective in hypertension. Enteramin is a dilator extract of the mucosa of the rabbit's stomach (49); it is distinguished by its properties from other substances such as histamine. There are two active substances in mistletoe which lower the blood pressure (50).



There is an excellent summary available on the actions of the pressor drug, veritol (51). Paredrine (52) through its constrictor action on peripheral vessels raises the blood pressure without causing changes in skin temperature or cardiac output, thus producing a condition which is very much like that in clinical hypertension. The vasopressor and other nicotinic actions of acetylcholine have been analyzed (53); the site of action is in the sympathetic ganglia.

When two drugs having opposite actions on the blood pressure, such as epinephrine and acetylcholine, are injected simultaneously or consecutively in suitable doses, the responses of the blood pressure depend on which drug is in excess and on the order of the injections (54). It is claimed that the effects on the vessels of the spleen, gut, kidney, and extremity remain unchanged despite a rise or fall or diphasic change in the blood pressure. Such results are interpreted as showing that in these drug actions an exaggerated significance has been attributed to the blood vessels in the regulation of the blood pressure (54).

#### THE VENOUS CIRCULATION

Elimination of the hydrostatic factor in the measurement of the brachial venous pressure, thus automatically securing a correct reference point, is accomplished by measuring with the subject first in the supine, then in the prone position (55). The venous pressure then equals one half of the sum of the two pressures. The position of the right atrium apparently is not affected by the shift in position. Values so obtained range from 7 to 14 cm. saline.

Constancy of peripheral venous pressure within a moderate range of variation in intrathoracic pressure, despite changes in right atrial pressure, is explained by a varying degree of collapse of the veins just before entering the thorax, thus affecting the resistance to venous flow (56).

The relation of the size of the venous channel to the rate of flow determines the level of venous pressure peripheral to that channel. This fact is used in simple exercise tests for the localization of venous obstruction in cases where the resting venous pressures may be little elevated (57, 58). Clinical experience in the prevention of venous thrombosis by accelerating the venous flow is supported experimentally by the effects of leg elevation and leg movements on vena caval flow in the dog (59).



The changes in venous pressure following thermal and mechanical stimuli and pressure on the carotid sinus and eyeball were attributed to changes in venous tone which was considered the determining factor influencing venous pressure (60). These conclusions ignored, however, the effects of changes in heart action on venous pressure. That a goodly number of the spontaneous waves in plethysmograms of the extremity are venous and not arterial in character (61) is indicated by the fact that raising the venous pressure in the observed extremity to 60 mm. Hg makes the spontaneous waves disappear without affecting arterial inflow. Neither do many of these waves occur simultaneously with changes in the latter; this observation is hard to square with the usual correspondence between waves in finger volume and finger volume pulse. Synchronism of the waves in the two hands would imply changes in venous tone due to vasomotor discharge. Disappearance of venous tone following high spinal anesthesia is indicated by the immediate decrease of venous pressure irrespective of the arterial pressure changes (62).

Krogh's hypothesis of the role of pituitrin in the maintenance of capillary tone finds interesting support in the extreme pallor of the skin without accompanying change in skin temperature, resulting from the slow injection of pitressin (63). This is considered to indicate a selective constrictor effect on the venules and capillaries without change in the skin arteries. The capacity of the veins to change in tone is probably decreased in senility due to senile atrophy of vein muscle (64).

#### THE VASOMOTOR SYSTEM

Many of the studies on vasomotor actions this past year are concerned with the specialized features of the circulation in different regions. It seemed best to discuss these papers in connection with these topics.

The concept of the vasomotor system as a blood distributing system rather than as a pressure regulating system implies that the vasomotor discharges are selective with respect to the vascular topography involved in the reactions. Many observations in the past support this concept. The discharges may also be selective with respect to the portions of the arterial tree; that is, the minute arteries may constrict but not the larger arteries. Thus, the larger hand arteries (digital and dorsal metacarpal) do not ordinarily participate in vasoconstrictor reflexes in the hand (65).



The cutaneovisceral vasomotor reflexes to the gut and skin elicited by heat or cold to the skin are segmental; they are elicited when the cutaneous vessels respond, this fact suggesting that the receptors are associated with the latter (66). The vascular reactions in the finger to local chilling (67) are dominated by the vasomotor reflexes set up; the reactive dilatation occurs whether vasoconstrictor paralysis exists or not.

It is claimed that the pressor responses to epinephrine and to vasoconstrictor impulses require the presence of an epinephrine complex which sensitizes the end organ (68); this complex is supposed to be formed following the continuous secretion of epinephrine in active form.

A comparison of the cold-pressor and breath-holding tests of the reactivity of the blood pressure shows statistical agreement but marked differences in individual performances (69). These differences are also observed frequently in the student laboratory during the routine performance of these tests; the discrepancies may be due to the inability of subjects to follow a wholly standard procedure in holding the breath. Vasomotor reflex time (reaction time) is lengthened about one third in senile subjects (70).

Whether pressor or depressor effects result from electrical stimulation of the forebrain (hypothalamus proper and areas surrounding it) depends on the frequency of the stimuli; reversal of effects may be obtained by altering the frequency (71). The rise in blood pressure during the excitement stage of ether anesthesia is prevented by sympathectomy (72).

Rotatory as well as caloric stimulation of the labyrinth in the morphinized rabbit increases the blood pressure and inhibits the action of the moderator nerves, but only when morphine is used; otherwise the rather well-known depressor effects are obtained (73). Local narcosis (produced by urethan or cocaine) of the aortic nerves results in a temporary fall in blood pressure at the beginning of narcosis (74). The carotid sinus depressor reflexes are weakened by coramine (75).

Certain vasomotor reflexes are discussed in the chapter (p. 407) in this volume by Hare & Hinsey on the autonomic nervous system.

*Vasomotor disturbances.*—Vasomotor reactions and blood flows are normal in the feet in schizophrenia (76, 77), but the reduced flows in the hands (77) are attributed to excessive vasoconstrictor



activity there. This difference implies a selective disturbance in the vasomotor discharges. This is probably also the case when trauma produces the symptoms of vasospasm in the affected part (78); hyperactivity of the vasoconstrictor supply there is indicated by the relief of symptoms resulting from blocking or section of the sympathetic supply to the part. The vasoconstrictor reflexes in the toes are weakened in peripheral neuritis; they respond earlier to thiamin therapy than do the somatic fibers (79).

*Muscle.*—Although vasomotor effects on the muscle circulation are small compared to the more active areas in the extremities and the splanchnic bed, they are important. Vasoconstrictor reflexes elicited by carbon dioxide administration are effective in the resting muscle when its circulation is adequate, but they do not act here when the muscle is active or when its circulation has been decreased by graded occlusion (80). This is taken to show that vasoconstrictor reflexes may be prevented from acting by the metabolic state of the organ. The general application of this principle would not seem admissible under physiological conditions.

Rein's observation that stimulation of vasoconstrictor fibers to muscle decreases the oxygen consumption of muscle may be reinterpreted as due to a redistribution of blood flow through the muscle (81), the blood following arteriovenous shunts. Hence, the changes in arteriovenous oxygen differences may reflect alterations in the intimate circulation rather than in the metabolism of muscle. This point deserves emphasis when arteriovenous oxygen differences are used either as an indication of the metabolism or of the circulation in an organ.

Both vasoconstrictor and vasodilator responses occur in the human forearm and calf (in which changes in the muscle circulation are probably dominant) following the usual vasoconstrictor stimuli (82). The vasoconstrictor responses are abolished by sympathectomy and so also are the immediate dilator effects, but delayed vasodilator responses continue after sympathectomy, suggesting that they are due to epinephrine. In trials on two cases of hypertension, denervation of the adrenals destroyed the delayed dilator response; this is an interesting, almost direct, support for the theory of epinephrine secretion in man.

The reactive hyperemia following a five-minute ischemia in the forearm and calf results in complete dilatation and is little affected by moderate vasomotor activity, although strong constrictor



stimuli may overcome it (83). This is in line with the observation that carbon dioxide seems to be much more effective in regulating the muscle circulation than is its vasomotor supply (84). However, relief of intermittent claudication by lumbar sympathectomy (85) indicates that a continued high sympathetic tone may overcome the dilator effects of muscle metabolism on its own circulation; development of a good collateral circulation must modify this interpretation.

Studies on the effects of training on human muscles working with and without blood supply suggest that the gain in work capacity must be largely due to enlargement of the muscle vascular bed since the ischemic work capacity is not greatly affected (86). The slowness with which the gain in circulated work capacity proceeds would indicate an actual growth of new vessels instead of simple dilatation. Liberation of potassium may be one of the factors explaining the hyperemia of muscular work; the amount of potassium required is relatively small (87). Among the possible dilator substances which occur in muscle, adenosine triphosphate seems significant; its action is about 140 times more powerful than that of adenylic acid (88).

The dynamics of the circulatory system during exercise have been exhaustively studied (89).

*Gastrointestinal tract.*—Distention or stretching of the intestine is followed on release by a brief hyperemia which is neither reactive nor due to a sudden inflow into empty vessels previously compressed by the inflation (90, 91). The hyperemia may be due to compensatory intrinsic reflexes elicited by the stretching. The flow in the intestinal mucosa in man, measured by means of a heated silver button carried on the surface of a balloon, increases during contractions and with the sight and smell of food in fasting subjects (92). Interestingly, emotional states, as anxiety and resentment, which have generally been considered as decreasing flow, may actually increase it.

*Liver.*—The study of the liver circulation is complicated by the fact that controls are exercised at at least three points: hepatic arterial inflow, portal venous inflow, and hepatic venous outflow. Hence, single determinations of liver flow (inflow or outflow) can have little significance. Differences between inflow and outflow are often cyclic in character, thus indicating cyclic storage and discharge of blood from the liver (93). Hepatic arterial inflow



tends to be more or less proportionately increased when portal flow is reduced. The complexity of vascular reactions in the liver is illustrated in the following description of the action of acetylcholine (94): Constriction of the hepatic venules in a peristaltic-like manner increases hepatic outflow temporarily and raises the resistance to inflow; this is followed by dilatation of the sinusoids and portal veins and increase in liver volume. On release of the hepatic venous resistance this accumulated blood gushes out at a rate determined by the dosage of the drug.

Contraction of the sublobular veins has the effect of a sphincter mechanism (95) by closing small sluice channels which are peculiar endothelial tubes formed from some of the liver sinusoids and which empty directly into the sublobular veins. As a result, the blood is shunted into the central veins, outflow is reduced and liver volume increased. The sublobular veins are constricted by large doses of epinephrine, by mecholyl, pilocarpine, and physostigmine and relaxed by small doses of epinephrine and by atropine.

Bile flow and hepatic blood flow do not necessarily parallel each other; the choleric substances, e.g., the conjugated cholates, do not increase hepatic flow while the hydrocholeretic substances, e.g., sodium dehydrocholate, do (96).

*Spleen.*—The widely accepted concept of the spleen as a blood reservoir—in large part due to the work of Barcroft on animals—has been challenged (97). The responses of the blood volume, hematocrit, and hemoglobin to exercise, epinephrine, and hemorrhage, all of which cause splenic contraction in the dog, are no different in the splenectomized man than in normal man. The less advanced development of the splenic musculature in man as compared with that of the dog may result in the spleen's behaviour as an elastic rather than as a contractile organ in man (98). The partly denervated exteriorized spleen is darker and free from the sinus cycles (99), which may mean that these depend on the innervation. Reciprocal relations are claimed in the reservoir functions of the spleen and lungs under the action of certain drugs (100).

*Cutaneous circulation.*—A promising method for calculating total cutaneous blood flow is based on the helium uptake through the skin (101). The skin flow is minimal and quite constant at temperatures below 28° C. but rises above this temperature to reach a value of 16 l. per hr. per sq. m. of body surface at 35° C.



The flow so determined agrees quite well with values calculated from heat elimination.

Quantitation of the strength and duration factors in the mechanical stroking of the skin permits calculation of an index of excitability for the tache by means of which the reactivity of the minute vessels may be compared in different subjects (102). The excitability is decreased by anoxia, increased by hypercapnia. The effect of vasodilator and vasoconstrictor influences on the latent period of dermographism is attributed to changes in the tonus of the skin capillaries (103), although the effects of reactions of skin venules and arterioles have not been excluded.

The dermovascular effects of estrogen (104, 105) are of three types: one, negative; two, "flush" type, involving increased blood flow and blood content of the skin, similar to the menopausal flushes, and not shown by men; three, "plateau" type, with no increase in flow but with a well-sustained increase in the blood content of the skin—dilatation beyond the arterioles—most marked in men. The "plateau" type and the negative type result when clinical relief is obtained in the menopause. The depth of skin blood color has some connection with the incidence of skin cancer (106).

The skin resistance response in man appears to have a vascular as well as a sweat gland component (107).

The application of more advanced observational methods in the analysis of the vascular actions of drugs is illustrated in an elaborate exhaustive study with photoelectric methods of the actions of epinephrine, amyl nitrite, histamine, veritol, etc., on the skin circulation (108). Selective actions with respect to different regions of the skin and also with respect to effects on skin arteries and veins are exhibited. The independence in effects on skin blood flow and skin blood content is most striking.

The vasoconstrictor effects of smoking on the skin have been attributed to the deep breathing rather than the nicotine content of the smoke (109), since smoking denicotinized cigarettes may be as effective as the smoking of standard brands. The ease with which constriction is induced in the skin of the extremities should caution one against transferring this result to other vascular beds.

Skin dilatation is induced by aminophylline (110) and by nicotinic acid (111, 112, 113). The former increases heat losses.

*The central nervous system.*—Total cerebral blood flow in the



monkey ranged from 0.36 to 0.77 cc. per gm. brain per min. (114); it was increased by caffeine, histamine, mechohyl, carbon dioxide, and metrazole and decreased by epinephrine (intracarotid) and ergotamine. Anoxemia had little effect. A qualitative indication of cerebral flow in man is supplied in the rate of increase in jugular venous pressure on applying compressing pressure to the neck with a cuff (115); the results of various procedures are in qualitative agreement with previous publications.

Cervical sympathetic stimulation increases the tone of cerebral vessels, but the variable results on flow are due to simultaneous effects on the intracranial and extracranial vessels with resultant shunting (116). The cerebral vessels became hypersensitive to epinephrine after cervical sympathectomy.

A form of local homeostasis results from the neurons' acid metabolites' dilating the vessels; the dilatation tends to increase the local pH and so restore equilibrium (117). Anoxemia raises cerebrospinal fluid pressure. There are two components in this rise: first, the reactions of the cerebral vessels; second, increase in brain volume resulting from edema due to injury to the cerebral capillaries (118). The tendency of cerebral vessels to dilate with anoxemia is difficult to reconcile with the moderate decrease in cerebral blood flow which is induced by insulin hypoglycemia in man (119), in which there is a large decrease in oxidations.

Age decreases the reactivity of the cerebral vessels to histamine, as measured by the rise in cerebrospinal fluid pressure (120). The actions of a number of drugs on pial vessels have been studied with a window technique (121).

An elaborate, comprehensive study on the mechanism of headache (122, 123) shows that this can be produced by traction on intracranial and extracranial vessels and also by distention and dilatation of intracranial and extracranial arteries.

*Bone.*—Sympathectomy decreases the blood supply of bone, probably due to the shunting of blood to the soft tissues (124). In perfusion experiments, epinephrine, acetylcholine, and sympathetic stimulation constrict while pilocarpine and papaverine slightly dilate the bone vessels (125).

*Fetal circulation.*—Closure of the ductus arteriosus is muscular and is initiated ordinarily by breathing (126). This is then followed by histological changes requiring about a month for completion and resulting in the formation of a fibrous cord. It is thus possible



that a patent ductus arteriosus may be due to failure of the normal functional method of closure rather than to a developmental anomaly.

*Metabolic rate and circulation.*—Forearm and calf blood flows are increased with a rise in the basal metabolic rate (127, 128), but there is no correlation between the latter and hand blood flow (127, 129). The toe temperature, however, parallels the metabolic rate quite closely (129). Failure of the hand flow to run parallel may be related to a high level of vasomotor activity in the hand; it is claimed that thyroxine stimulates the vasomotor centers for the skin (130). It is possible that the increase in forearm and calf flow in hyperthyroid cases may be due to growth of the vascular bed in muscle rather than vasodilatation there. Thus, reactive hyperemia in muscle is greater during the period of hyperactivity of the thyroid (128); there is an increase in the blood volume (131); and the slow return of the blood flow to lower levels after thyroidectomy and after administration of Lugol's solution (127, 128) would favor this view.

Total cutaneous blood flow, calculated from heat elimination data, parallels the basal metabolic rate (132). Shortening of the circulation times is again confirmed (132, 133). A reduction in the peripheral resistance (132), as calculated from the arterial blood pressure and skin flow, is in line with the suggestion expressed above that hyperplasia occurs in the vascular bed of muscle.

Blood flows in the hand, forearm, and leg are little affected by meals (134). This result may seem remarkable in view of the subjective sensation of skin warmth which has also been demonstrated objectively, and in view of previous measurements with the thermostromuhr on the femoral and carotid arteries of the dog.

*Posture.*—Circulatory insufficiency which would result from the effects of gravity on the circulation (135) may be compensated for by several mechanisms: First, maintaining the venous return eliminates the need for extreme vasoconstriction. Postural sway may sufficiently aid the venous return so that extreme splanchnic vasoconstriction does not occur (136); the latter may be so extreme in rigid standing as to interfere with gastric secretion. Aiding the venous return by inversion of the dog may be enough help to offset shock (137). Second, redistribution of the circulating blood by vasoconstriction in the extremities (135, 138, 139, 140), particularly in the lower extremities, conserves the falling cardiac output for more vital areas. Constriction in the lower extremities



may not prevent the pooling of blood there in the absence of postural sway or movement. The moderator nerves are necessary in the dog (141) but not in the rabbit (142) to compensate for the feet-down position.

Orthostatic hypotension has been explained as due to failure in the vasomotor reflexes in the extremities (138, 140), such cases showing absence of these reflexes to stimuli such as startle, cold, etc. These cases do not show excessive pooling of blood in the lower extremities. However, a very large decrease in the circulating blood volume (possibly due to splanchnic pooling) must contribute greatly to the circulatory deficiency (143). The difficulty of these cases has also been attributed to a diminished venous return; they give a reduced Flack test; failure of the vasoconstrictor reflexes is denied (144). Very fine therapeutic results were obtained by having the subjects sleep in the head-up position.

#### CAPILLARIES, TISSUE FLUIDS, AND LYMPH

Blood pressures in the forearm capillaries measured by a pressure plethysmograph agree closely with the values determined by a direct micro method (145). It is surprising that these values were unaffected by thermal dilatation or reactive hyperemia.

Although contractility of capillary endothelium has been considered as having little significance in the mammal, endothelial swelling sufficient to obliterate the lumen may be promptly elicited in the rabbit's ear by sympathetic stimulation (146). A capillary sphincter mechanism at the origin of the capillary is described in the frog (147); this sphincter may act with the arteriole or independently, thus controlling the flow through the rest of the capillary. The progressive changes in flow in the capillary bed in response to injury have been systematically studied (148, 149).

Surprisingly consistent results are reported for capillary fragility determined by the suction method (150, 151). Increase in capillary fragility in diseases of internal organs occurs in those dermatomes receiving their innervation from the same segment of the cord as the affected organ (150). Both vitamin C (152, 153, 154) and vitamin P (155, 156, 157) restore capillary resistance to normal, vitamin P seeming to be somewhat more effective (157).

Inverse relations between capillary permeability and blood



flow (within limits) are indicated in the results of perfusion experiments on the knee joint (158); the capillary permeability was decreased by sympathectomy which increased the flow. The capillary permeability factor of normal tissues and of inflammatory exudates is correlated with the histamine activity (159); however, dialyzed tissue extracts regain their effectiveness on the addition of leukotaxine in the absence of histamine (160). Efficacy is not restored by the latter. Care in the interpretation of permeability phenomena in inflammation is indicated by the results of experiments in which the changes in permeability are divorced from leukocytic infiltration (161). Estimation of permeability changes from the passage of dyes into the inflamed area is confused by the injured cells' holding the dye, thus making the injured area visible (162). There need be no correlation between the intensity of the coloring, and edema and hyperemia in the area.

The very rapid passage of water through the capillary wall is indicated by studies with heavy water (163); thirty seconds after injection the heavy water had been diluted by a volume of fluid equal to that occupying the extracellular spaces. The movement of sodium (radioactive) is slower, diffusion equilibrium requiring two hours (164). The diffusion equilibrium between blood and synovial fluid is reached somewhat later (one to four hours) than that between blood and the extracellular compartment (165). Since this is also the case for edema fluid and since normal synovial fluid is a dialyzate of blood plasma (166), the slowness in reaching equilibrium is probably due to the mass of synovial fluid as well as the slow circulation in the synovial membrane.

Calculation of the extracellular volume from the distribution of injected radioactive sodium gave values of 25 to 29 per cent of the body weight (164). These values agreed with those calculated from sulfocyanide injections. The method offers important advantages: it is quick, accurate, and nontoxic. The use of chloride and sulfocyanide for the determination of the extracellular volume gives values which are too large, due to these substances moving inside cells, particularly in the stomach, intestine, spleen, and pancreas. Infusion of glucose or saline may alter the distribution of both substances, so that also in this case they cannot be used for calculating the effect of the infusion on the volume of the extracellular fluid (167).

Structural conditions affecting the interstitial fluid are indi-



cated in the intermittent uptake of fluid injected under low pressure by means of a micropipette (168). The intermittence continues in hyperemia. When a certain injection pressure is exceeded (the "breaking point"), the tissues give way as though formed elements were separated, and the uptake becomes continuous. It is also continuous in edema, this fact showing that in this case the interstitial channels are established and the flow of fluid is free. The sexual swelling of the baboon is also an expansion of the extracellular compartment although the water does not appear to be in the state of a simple edema (169).

The one instance in the body in which lymph and blood serum have the same protein content is the case of the liver and gall bladder lymphatics (170). The composition of the two lymphatics is identical, this fact indicating that these two groups of lymphatics are connected freely and extensively. Presumably, the liver cells are either bathed directly in the blood plasma or are separated from it by an extremely tenuous membrane.

Anoxia, produced by decreased blood oxygen or carbon monoxide (171), and hyperthermia (172) increases cervical lymph flow, probably due to capillary damage.

#### BLOOD VOLUME

Two methods for the determination of blood volume have been based on the use of radioactive elements, one on phosphorus (173), the other on iron (174). The latter method gives smaller values for the red cell volume than that calculated from hematocrit and plasma volume determinations. This difference appears to be due to the process of plasma skimming in the minute vessels, so that the hematocrit of a sample of blood removed from an artery or vein is not representative of all the blood in the vascular system (175). A gasometric method is based on the distribution of nitrogen between blood and lung air (176). Improvements have been made in the carbon monoxide method (177).

Modifications (178) and improvements in the dye methods (179) have value but do not eliminate the errors due to nonrepresentative hematocrits (175). Actual estimation of the passage of the blue dye T-1824 into the lymph (180) does not indicate that the escape of dye in the first few minutes after injection introduces much error in the determinations. Exercise, however, alters the



optical properties of the serum sufficiently to lead to large errors (181).

Important seasonal changes occur in blood volume in relation to acclimatization (177), the larger volumes paralleling the rise in outdoor temperatures. Much smaller effects (irrespective of race) have also been reported although the colored sharecropper of the South had about 25 per cent more interstitial fluid than the whites (182).

Blood volumes decrease on standing (177), the fall being excessive in orthostatic hypotension (143).

Hemoconcentration without addition of cells occurs in moderate exercise (183); exhaustive exercise appears to add new cells. The existence of noncirculating reserves of red cells or plasma in man has been challenged (97). If true, this difference between dog and man may explain the paradoxical concentration of the blood which occurred immediately after the injection of concentrated plasma in the dog (184); the expected dilution took place in the splenectomized animal.

Values for the blood and plasma volumes determined by improved methods are available for normal infants and children (179, 185).

#### SHOCK

The experimental study of shock has lagged far behind the efforts at therapy. Starting with the well-established fact of a decrease in the circulating blood volume, the major effort has been made in the direction of perfecting the technique of preparation and administration of blood, plasma, and serum. This subject is beyond the scope of this paper.

Work on the physiology of experimental shock has largely repeated and confirmed the experiments and positions taken in the past. Thus, the theory of initiation of shock through local fluid loss is supported by the results of trauma and burns (186, 187), and by the presence of sufficient fluid in the peritoneal cavity in intestinal strangulation to account for the decreased plasma volume (188). That the capillaries in the injured area are excessively permeable is indicated by the great increase in the local fluid loss and the large loss of plasma protein following massive doses of saline (187). The local losses are less with plasma. Not all of the fluid lost from the blood stream could be accounted for by the local fluid loss, this finding implying a generalized increase in the



capillary permeability. Obvious general capillary injury appears late, however (186, 189). Theoretically, it is not necessary that the initial increase in capillary permeability be visible to morphological techniques. The plasma loss produces shock through decreased circulating blood volume since uncomplicated hemoconcentration (without decrease in blood volume) does not lead to shock unless the increased viscosity slows the circulation (190).

The existence of a generalized anoxia, which results from the vicious circle of shock, is supported by the beneficial effects of oxygen therapy (191, 192, 193). The damaging effects of a rise in body temperature in shock (194) are probably due to aggravation of the anoxia by the increased metabolic rate although a shift in blood to the skin may be at the expense of the vital centers.

The toxic theory of shock has again been negated by the failure of sterile autolyzing implants of liver or muscle to develop shock in rabbits although some local fluid loss did occur (195). It is possible that the rate of absorption (of hypothetical toxic substances) may have been too slow in these experiments. Blood from legs damaged by tourniquets applied for six hours (a procedure known to produce shock when the tourniquet is released) does not contain an excess of toxic substances, judging by the death rate of adrenalectomized mice when injected with this blood (196). The production of a highly diffusible dilator substance in the frog by localized microinjury (148, 149), as well as the results of exchange-transfusion experiments in the dog (197), indicates that the toxic theory must still be considered a possibility.

The possible role of histamine in the development of shock finds support in the early rise of blood histamine in wheal formation (198), in the liberation of histamine from liver in sufficient amount in peptone shock to account for the degree of shock (199), and also in a sustained increase of gastric secretion in burn shock (200). There seems to be no correlation between the degree of histamine shock and the dosage of the drug (201). Tolerance of rats for histamine, which is extraordinarily high, is decreased by hypophysectomy and adrenalectomy and increased by desoxycorticosterone (202). Cervical lymph flow increases early during histamine shock in the dog and then diminishes (203); these variations were considered as showing corresponding changes in capillary permeability.

The theory of the genesis of shock through hyperactivity of the



sympathetic nervous system (vasoconstriction, epinephrinemia) is again supported in the shocking effects of prolonged continuous injection of epinephrine in unanesthetized dogs (204). A contradiction of these experiments is implied in the exaggerated pressor response to epinephrine during the development of traumatic shock (205); these effects might be due, however, to a momentarily increased outflow from the liver (95) restoring the cardiac output against a high resistance. The slow absorption of epinephrine (intramuscular injection in oil) maintains the arterial blood pressure and increases survival in cats subjected to intestinal manipulation (206). These pressor effects of epinephrine tend to reopen the question of the use of vasospastic drugs in shock. Reduction of blood flow in an uninjured extremity is reported as occurring before hemoconcentration (207); the failure of sympathectomized dogs to go into traumatic shock (providing blood losses into the injured area are minimized) is associated with an adequate peripheral circulation. Increase in the circulation time is confirmed (208, 209).

The general disfavor with which vasospastic drugs are viewed in the treatment of shock does not conform to the beneficial effects of pituitrin and epinephrine in experimental shock (205, 206, 210). There is need for analysis of the hemodynamic actions of the pressor drugs in circulatory failure. Thus, veritol and otrivin increase blood pressure and peripheral resistance and decrease arterial elasticity and the minute volume (211, 212); neither would seem desirable in shock because of their effects on the cardiac output. The pressor effects of veritol tend to disappear with the onset of shock.

Continued success is reported in the use of adrenal cortex preparations in the prevention and treatment of experimental shock (213, 214, 215). Clinical experience is more limited but favorable, cortex decreasing the permeability of the capillaries of shocked patients who now show improved retention of injected plasma (216). Desoxycorticosterone was found to have little value in human cases (217), although it did prevent circulatory collapse in the dog from muscle trauma (215).

It is curious that thiamin increases survival in shock induced by hemorrhage with pressor effects on the blood pressure (218); it constricts the blood vessels in the frog (219).



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DEPARTMENT OF PHYSIOLOGY  
ST. LOUIS UNIVERSITY SCHOOL OF MEDICINE  
ST. LOUIS, MISSOURI



## HEART

BY MAURICE B. VISSCHER

*Department of Physiology, University of Minnesota,  
Minneapolis, Minnesota*

*Chemical energetics and chemical composition.*—The problem of the sources of energy for cardiac contraction constitutes a central question in the physiology of the heart. The ultimate energy source is clearly the oxidation of carbon and hydrogen in certain food-stuffs. No convincing evidence exists that amino acids are burned for energy in mammalian heart muscle. Carbohydrate and fat remain as the possible sources of oxidative energy. The disappearance of carbohydrate and lactic acid does not account quantitatively for the oxygen consumption of the heart in isolated preparations particularly when the glucose level in the perfusion fluid is low. Consequently studies of fat metabolism in relation to cardiac activity are of fundamental interest. New observations (1) on the losses in glycogen, glucose, phospholipid, cholesterol, and neutral fat, from the heart and the blood of the rat heart-lung show that in this preparation, when the blood sugar is low, a very appreciable and regular decrease in blood and muscle neutral fat occurs. No change in other lipid components is seen. The decrease in neutral fat is greater with increased load on the heart. Unfortunately the lungs were not analyzed and the oxygen consumption was not measured, consequently an energetic balance cannot be calculated, and some doubt still remains as to whether fat might not be stored in the lungs. Nevertheless these observations constitute the first clear proof that the neutral fat in the blood and heart muscle declines in the perfused heart-lung preparation and are highly significant. Numerous earlier observations prove that in the intact organism the energy from fat combustion is available for muscular work. Critical proof of a positive character that muscle tissue is able to utilize fat oxidation energy has been lacking.

The intermediary metabolism and chemical composition of the heart have received considerable attention particularly in relation to cardiac failure and the influence of drugs upon it. The rate of turnover of phosphate in slices of heart muscle of the dog has been studied with the radiophosphorus tracer technique (2). It was found that the exchange of phosphate in hexose monophosphate is



about one fifth as rapid as in phosphocreatine and adenylypyrophosphate. For the latter two compounds exchange was 50 per cent complete in 40 min. at 37.5° C. The values given refer to the proportion of phosphate exchanged for each substance. Further application of this method may be anticipated to yield important information concerning the intermediary metabolism of heart and other muscle tissues.

Direct determination of creatine in right and left ventricular muscle in thirteen human subjects after sudden death showed 203 and 165 mg. per 100 gm., as compared with 443 mg. per 100 gm. in the pectoralis major muscle (3). The corresponding values for potassium were 285, 219, and 328 mg. per 100 gm. and for acid soluble phosphorus were 194, 160, and 201 mg. per 100 gm. For each component the order of concentration differences in the three tissues is the same. Water content was greatest in muscle of the right ventricle and least in skeletal muscle. Studies on the carbohydrate content of human hearts at autopsy following death from various conditions are reported for forty-nine cases (4). Glycogen and lactic acid were separately determined. The latter is elevated in cases presenting acute and especially chronic anoxemia. Other studies on the glycogen content of heart muscle show that castration brings about a decrease and that testosterone injection increases the level above control values (5).

Heart muscle contains more thiamin than skeletal muscle, the quantity in mammalian ventricle ranging from 80 to 170 I.U. per 100 gm. (6). Atrial muscle contains less than one half as much. The influence of ascorbic acid on the amount of glycogen in the heart has been studied (7). A study is reported of the production and metabolism of citric acid in heart muscle and other tissues (8). Heart muscle possesses the greatest capacity for synthesis of citric acid from pyruvic and malic acids. Heart muscle and liver contains less citric acid than the blood whereas mammary gland, kidney, and other glands have much higher values.

The accumulation of carbohydrate metabolites in the production of cardiac abnormalities has been studied in thiamin deficient rats (9). It was found that accumulation of intermediary carbohydrate metabolites is probably not an important causal factor in the production of cardiac abnormalities in beriberi. Some defect in metabolism other than accumulation of metabolites is a more probable cause of such disorders.



The copper and zinc contents of human heart and skeletal muscle have been measured (10). The average copper content is 13.4 mg. per kg. of dry matter in heart and 6.4 mg. per kg. of dry matter in skeletal muscle. Zinc averages 100 mg. per kg. of dry matter in heart and 226 mg. per kg. of dry matter in skeletal muscle. The differences are statistically highly significant. The observations were made on Chinese subjects shortly after death; no reference was made to cause of death. Blood studies show low zinc values in undernourished subjects.

Cardiac muscle from cats, in which alkalosis was produced by intraperitoneal injection of sodium bicarbonate solutions, shows increases in potassium and phosphorus content but no change in total water or its distribution (11). Further chemical studies on human necropsy material confirm the occurrence of a decrease, averaging 27 per cent, in the creatine content of left ventricle muscle in persons dying with congestive heart failure, as compared with that in persons dying suddenly of unspecified causes without obvious cardiac abnormalities (12). Somewhat smaller declines in total phosphorus and potassium are noted. A breakdown and loss from the muscle of dipotassium phosphocreatine would account for the major part of the changes. An excess loss of potassium and phosphorus remains, however. Extractive purine nitrogen has also been studied and found to decrease. All of these components occur in higher concentration in left than in right ventricular muscle. Studies on rat hearts made hypertrophic by thyroid feeding show no change in the chloride space in the myocardium (13).

*Work capacity and physical properties.*—The increment in diastolic fiber length produced by a given increase in load of work imposed upon a heart is in general an inverse measure of its work capacity. If the load is increased by an elevation in the pressure against which a heart is made to pump a constant stroke volume, the ratio  $\Delta V/\Delta P$  can be employed as an index of work capacity. This ratio rises with time in isolated hearts. Recent studies show that when the dog heart in the heart-lung preparation is supplied with insulin and glucose, the latter at a rate of 0.15 mg. per gm. per min., the  $\Delta V/\Delta P$  ratio has about one half the value it would have without such treatment (14). The action of certain drugs has been analyzed by a study of effects upon this ratio (15). Veritol greatly decreases the ratio. The age of the heart preparation determines the amount of decrease. The extent of deterioration of the



isolated heart preparation, that is its spontaneous failure, can be measured in terms of changes in the  $\Delta V/\Delta P$  relationship.

The diastolic and systolic elasticity of the mammalian heart have been studied (16). The elasticity in systole is about two-hundred times the value in diastole. It is further shown that diastolic elasticity is a varying function so that other factors besides the atrial filling pressure determine the diastolic ventricular volume. On account of the occurrence of hysteresis and elastic fatigue the previous history of the ventricle determines the diastolic elasticity at any point in time during that phase. Veritol increases the systolic and decreases the diastolic elasticity of the ventricle (15).

The action of the renal pressor substance directly upon the heart has received attention. The demonstration (17) and confirmation (18) of such effects, particularly upon the work output of the isolated heart, are reported. The relative importance of the vascular and cardiodynamic effects of the renal pressor agent has not been established, but it is now necessary to take into account the actions upon the heart itself in considering the pathological physiology of renal hypertension.

Therapeutic doses of digitalis, cardiazole, coramine, hexetone, and strychnine injected into normal humans had either no or very slight effects upon pulse rate, blood pressure, or minute volume output of the heart (19). In the case of digitalis, with a dose equivalent to 100 mg. of leaf, the mean change in six trials in minute volume of the heart was from  $3.80 \pm 0.31$  l./per min. to  $4.05 \pm 0.20$  l./per min. thirty minutes after injection. The acetylene method was employed. The results are of especial importance because certain earlier workers had reported a decrease in cardiac output in normals in contrast to increased outputs in heart failure following digitalis administration. The discrepancies between the results of various workers may be due to one or more of several factors: (a) Difference in method of measurement; (b) differences in dose levels, larger doses bring peripheral vascular effects into more prominence; (c) time after administration at which studies are made, since compensatory reflex changes may come into play.

Further studies of calcium ion effects on the frog heart confirm the increase in "systolic tone" and show an increase in duration of systole (20). Excess potassium ion causes a decrease in duration of systole. Water moccasin venom in concentrations greater than 1:1,000,000 decreases the amplitude of contraction of the isolated



frog heart (21). Higher concentrations produce arrest in partial or complete contracture.

The time relations of systolic pressure rise in relation to spread of excitation have been studied in the turtle ventricle (22). The steep portion of the intraventricular pressure curve apparently follows the complete excitation of the entire ventricle. Earlier excitation, "fractionate contraction," of portions of the ventricle is responsible for the initial slow rise of pressure during systole.

Measurements of intramyocardial pressure from an imbedded artery segment show a drop when the venous inflow into the heart is increased in the intact animal, and also after vagotomy (23). Although the observations are obviously valuable, the reviewer cannot follow the reasoning of the authors in deducing from this and similar observations that "increasing the initial length of muscle fibers . . . results in a diminution in the force of its contraction" and vice versa. In considering the functional significance of these observations the concept "force of contraction" must be scrutinized. In a loose way, work capacity and force of contraction have frequently been used synonymously. If they are so used neither the intramuscular nor the intracardiac tensions are their sole determinants. It is obvious on physical grounds that the larger the surface area of a contracting cavity the smaller need be the tension per unit area of fiber to accomplish a given amount of work in shortening the fibers, in other words, decreasing the cavity area to a constant minimum or systolic volume. The energy available for work in expelling blood under tension depends upon the surface area of the cavity undergoing contraction as well as upon the force exerted per unit area. Since there is no doubt that work performance is actually increased when the diastolic fiber length increases it is apparent that the force utilized in doing work upon the blood is increased and not decreased, and that the statement quoted above is misleading.

*Cardiac activity in exercise and low oxygen tension.*—Exercise for one to two hours per day for forty-six or more days at lowered oxygen tensions equivalent to 20,000 ft. altitude does not produce significant cardiac hypertrophy in guinea pigs (24). An x-ray kymographic study of nearly five hundred athletes engaged in various sports is reported (25). This work provides valuable data for comparison with nonathletic controls, which were, unfortunately, not included in the study. Serial electrocardiographic stud-



ies during athletic training were made during one season on forty-eight subjects. Of these, four showed minor changes of obscure significance (26).

Studies on normal humans and patients with cardiac disease breathing gas mixtures containing variable proportions of oxygen, carbon dioxide, and nitrogen have indicated that addition of 3 per cent carbon dioxide to low oxygen mixtures tends to prevent the manifestation of the signs of partial anoxia upon the heart (27). The subjective improvement upon addition of carbon dioxide to low oxygen mixtures is probably due largely to effects upon the blood flow to the brain, but the changes in the T wave of the electrocardiogram and the disappearance of pain in patients with angina speak for a direct effect upon the oxygen supply to the myocardium. This effect might result either from a coronary dilatation or from a shift in the dissociation curve of oxyhemoglobin.

It is observed that amphetamine increases the systolic blood pressure in man both at sea level and at a simulated altitude of 20,000 feet (28). The lowering of T wave voltage, produced ordinarily by partial anoxia, is prevented by amphetamine.

Measurements of the so-called "economy of effort index" in human subjects show that when air low in oxygen is breathed this index increases significantly in most individuals (29). The index is essentially a ratio of certain areas in a reconstructed intraventricular pressure curve (30). The "economy of effort index" is, therefore, not a measure of efficiency of the conversion of energy to work by the heart. It increases with the pulse pressure, and is as much if not more dependent upon the state of the peripheral circulation than upon cardiac activity. The authors are careful to say that the index measures the economy of utilization of mechanical energy, which excludes the efficiency of the heart in converting chemical to mechanical energy. That anoxia exerts any stimulating action on the heart itself is unproven, unless an increase in load, as indicated by the augmentation of cardiac output under conditions of oxygen want, is looked upon as a "stimulation." It will be necessary to show that changes in peripheral resistance are not entirely responsible for changes in the index in question before any stimulating action directly upon the heart muscle is indicated. Other studies bear upon this problem. An increase in pulse pressure under conditions of oxygen want has been observed in most normal men (31).



A decrease in peripheral resistance in most subjects has also been noted (32).

*Influence of respiration on cardiac function.*—Studies are reported of volume changes in the several chambers of the heart in relation to alterations of intrathoracic pressure (33). The right atrium becomes larger and the left atrium smaller in inspiration. The diastolic volume of the two ventricles together diminishes in inspiration. Since right atrial filling is increased it is argued that right ventricular filling should likewise be, and that, therefore, a decrease in left ventricular filling accounts for the net decrease in total ventricular volume in diastole. The ventricular volume was measured under circumstances which exposed those chambers to atmospheric pressure. Motion picture studies through a glass window appear to confirm the change in size of the left ventricle when exposed to natural pressure conditions. It is not certain that the same results would be obtained if the ventricle were exposed to the changing intrathoracic pressure.

In another investigation (34), an ingenious arrangement permitted measurement of ventricular volume under normal pressure relations. A recording tambour, open on one side to the intrapleural space and on the other to the cardiometer, was employed. With this arrangement it is found that in inspiration diastolic ventricular volume is increased and in expiration reduced. The effects are exaggerated by the deep and slow respiration of the vagotomized animal, and also by tracheal obstruction.

*Metabolic and endocrine relationships.*—Cardiac volume, as estimated from x-ray area measurements, is found to be reduced in six patients with corticoadrenal insufficiency (35). The reduction is greater during Addisonian crises. The blood volume, measured by the Congo red method, is not significantly reduced, except in a crisis. The results are particularly interesting because of the previously described effect of desoxycorticosterone in producing cardiac enlargement and failure.

No evidence of myocardial disease was seen in fourteen patients with myasthenia gravis (36). This observation is of some importance in connection with the problem of the fundamental disorder in the disease in question, and also on the problem of possible qualitative differences in the metabolism of skeletal and cardiac muscle. If the more fundamental chemical energetics of striated



and cardiac muscle are identical, as seems likely, the disorder in myasthenia gravis could not involve those fundamental chemical reactions. Disturbances in the excitation mechanism would be a more likely mechanism of the disease.

Mean basal pulse rates and other physiological variables are reported in Europeans living in the tropics for prolonged periods (37). Climatic rather than dietetic or occupational factors are believed to be responsible for changes from values observed in other situations.

Rigor is delayed in thyroidectomized rats (38). Cardiac glycogen is elevated after thyroidectomy. The control values for cardiac glycogen in these experiments are extraordinarily low. Thyroidectomized rats have been fed fresh thyroid gland from various sources and the effect on the heart rate noted (39). Glands removed surgically from patients with toxic goiter have a greater heart rate increasing effect than do normal glands. The difference is out of proportion to variations in basal metabolic rate effects of the thyroid feeding. In the presence of deficiencies of both potassium and vitamin B<sub>6</sub> in the diet, the rat heart shows characteristic lesions consisting of areas of necrosis (40). Electrocardiographic changes including increased conduction time and block are found.

The blood pyruvate is elevated from a normal value of 0.6 to 1.1 mg. per cent in eight subjects to 1.7 to 3.4 mg. per cent in eleven severely decompensated patients. After return to a state of compensation the values reverted to normal (41).

*Action of digitalis glycosides.*—The mechanism of action of the drugs of the digitalis series upon the heart has been studied from various angles. The administration of digitalis, in doses of 0.5 c.u. per day for one to five days, to cats weighing about 3 kg. results in an increase in heart muscle potassium from 61.5 m. eq. per kg. in the controls to 69.4 m. eq. per kg. (42). The chloride decreased from 35.2 m. eq. per kg. in the controls to 31.7 m. eq. per kg. in the digitalized animals. The calculated intracellular water content of heart muscle therefore increased in the digitalized animals. This calculation assumes zero chloride concentration in the muscle cells, which assumption has never been tested under the influence of digitalis glycosides or other active agents. Studies on glycogen, lactic acid, and total carbohydrate content of rabbit heart muscle show no significant changes following acute or chronic treatment



with digitalis bodies (43). Unfortunately the hearts were taken after death by stunning and bleeding, therefore the values observed are open to serious question. Changes in glycogen content as a sign of cumulative effect of digitalis have been studied (44).

The oxygen consumption of minced heart muscle is not changed in any consistent way by large or small doses of strophanthin (45). The anaerobic lactic acid production is also insignificantly altered.

In the perfused cat heart, neither oxygen lack nor carbon dioxide excess alters the binding of strophanthin from the normal (46). Poisoning with pilocarpine increases glycoside binding. The absolute amount of glycoside removed from the perfusion fluid is independent of concentration over the range of 0.66 to 3.3  $\mu\text{g. per cc.}$  Further studies of binding of digitalis substances by protein fractions of muscles are reported (47).

Previous thyroxine treatment of cats exerts very little effect upon their sensitivity to digitalis (48). Thiamin-deficient rabbit hearts and intact rats are somewhat more resistant to digitalis bodies than are the normal (49). Magnesium sulfate aggravates the impairment of conduction in the dog heart caused by toxic doses of digitalis, and increases the susceptibility to production of ectopic beats (50).

Administration of gitalin, in doses of 5 to 10  $\mu\text{g. per gm.}$  to mice increases tolerance to the lethal effects of low oxygen tension under certain limited conditions (51).

A study is reported of the action of a purified glycoside, lanatoside C from *Digitalis lanata*, in patients with congestive heart failure with normal sinus or irregular rhythm (52). The efficacy of digitalis therapy in the treatment of heart failure with regular rhythm is established. A method is described for the clinical utilization simultaneously of the rapid but transient effect of intravenously administered ouabain, and the slow but protracted effect of digitalis given by mouth (53).

An ingenious study of the role of hepatic venous constriction in digitalis action is presented (54). The liver and spleen were made radiographically visible with thorotrast in a patient with congestive failure showing a normal rhythm and the outlines of those organs studied after administration of 1.5 mg. digoxin. Both the liver and spleen diminished in size very appreciably within twenty minutes, coincident with the fall in venous pressure from 14 to 7



cm. of water. The observation is interpreted to "refute the view that the beneficial action of digitalis is due to its constricting effect upon the hepatic vein."

Studies in cats of the influence of structure upon cardiac action of the digitalis bodies show that digitoxigenin has a greater effect on the sinus rhythm than does the glycoside digitoxin (55). Likewise the genin has a greater effect, in proportion to lethal doses, on conduction time and block than does digitoxin. Gitoxigenin shows somewhat similar differences from its related glycoside desacetyloleandrin (56). The effect of various glycosides on the electrocardiogram is described (57). Studies of detoxification of digitalis in chick heart have been made (58).

The myocardial damage produced by digitalis glycoside overdosage in dogs is observed with lanatoside *C* only if the dose is at least 0.2 cat unit per kg. body weight daily for twenty or more days by intravenous injection (59). Such doses over many days are outside the therapeutic range and it is concluded that the type of toxic effect in question is probably not of clinical significance.

*Coronary flow.*—Valuable new studies have been reported on the role of the Thebesian veins and luminal vessels of the right ventricle on intracardiac blood flow (60). The pressure conditions necessary for flow from the right ventricle into these vessels were investigated by the use of perfusion fluids containing India ink or Berlin Blue. It was found that no gross or microscopic evidence of entrance of fluid occurs so long as the right intraventricular pressure is lower than the left, both during systole and diastole. In view of the normal pressure relationships it is concluded that under ordinary circumstances in the beating heart, blood from the right ventricle does not contribute to the nourishment of the myocardium, even of the right ventricle. The distribution of blood from the several coronary artery branches has been studied by an injection technique (61).

Observations on coronary flow by the thermostromuhr in the dog heart-lung preparation show that changes in cardiac inflow and output have no effect if the arterial pressure and temperature are kept constant (62). Cardiac sympathetic stimulation more than doubles the coronary flow, indicating a vasodilator function of these nerves, but acceleration of the heart by direct driving of the sinoatrial region also causes augmentation of coronary flow. The



increase under the latter circumstance is not as great as with sympathetic stimulation, for comparable changes in heart rate.

Simultaneous studies were made, on dogs under chloralose anesthesia, of blood flow in the right coronary and the circumflex branch of the left coronary arteries (63). The flow in the latter is on the average 2.7 times as great as in the former. In every instance, the direction of change in flow produced by drugs is the same in both arteries. Amyl nitrite, nitroglycerin, aminophylline, histamine, mecholyl, and papaverine increase the coronary blood flow, in spite of a reduction in arterial blood pressure. These substances therefore reduce the effective coronary peripheral resistance. This is, however, not equivalent to saying that the drugs in question are all coronary vasodilators, because the intracardiac pressures in both systole and diastole have determining effects upon coronary flow. Epinephrine increases both coronary flow and blood pressure. Pitressin increases blood pressure and greatly decreases blood flow. It is apparently a true coronary constrictor agent. Coramine (pyridine  $\beta$ -carbonic acid diethylamide) in these experiments increases blood pressure and coronary flow, but it must be noted that coramine dilates the heart, and that therefore the coronary flow effect may be due to changes in the extravascular tension in the myocardium. Confirmatory evidence is provided that, in anesthetized dogs, nitrites and xanthines increase the diastolic coronary flow, both absolutely and relative to the aortic pressure head (64).

Angiotonin decreases the coronary flow and increases the amplitude of contraction in the isolated cat heart perfused with Ringer-Locke solution (17). Renin has no such effect. In the heart-lung preparation, fed with blood, renin increased cardiac output. The importance of some component of the plasma to the occurrence of the renin effect is obvious. Angiotonin also increases the work capacity of the heart in the heart-lung preparation. No consistent heart rate changes were found. No changes in the electrocardiogram specifically referable to the effects of angiotonin on the heart are evident.

Distention of the stomach or peritoneal cavity in dogs ordinarily produces a reduction in coronary arterial flow in dogs as measured by a thermostromuhr applied to the circumflex branch of the left coronary artery (65). The effect was abolished in fifteen out of



sixteen trials by vagotomy or atropinization. The possible importance of such a reflex in patients with angina pectoris following ingestion of food is obvious. The occurrence of anginal pain is susceptible patients, when made to breathe 10 per cent oxygen, is more prompt after meals than with an empty stomach (66). Atropine abolishes the effect. In the dog it is found, using a Morawitz cannula technique, that the coronary sinus outflow is increased during induced skeletal muscle contraction (67).

A histological study of the ratio of capillaries to muscle fibers, and the concentration of capillaries per unit area of muscle tissue, shows that the former changes from 1:6 at birth to 1:1 at maturity, while the number per unit area of muscle does not change in normal hearts (68). During hypertrophy there is a decrease in capillary concentration, indicating a relatively less adequate blood supply to the enlarged muscle fibers. The increase in coronary arteriolar wall thickness found in a histological study of necropsy material from patients with malignant hypertension is less than the increase found in the arterioles supplying skeletal muscle (69). The myocardial fibrosis seen in this disease is ascribed to narrowing of the coronary vascular bed.

Cholesterol-fed rabbits show no microscopic evidence of myocardial damage (70). Two such animals studied nevertheless presented abnormal responses to the administration of low oxygen respiratory mixtures. Sixteen of twenty-two rabbits fed a high cholesterol diet developed severe atherosclerosis involving the coronary arteries (71). The average heart weight in these animals was nearly twice that of a control group. This cardiac hypertrophy is interpreted as resulting from the coronary sclerosis by virtue of the consequent ischemia. The possibility of a direct metabolic effect of cholesterol feeding on the heart muscle or an indirect one through an endocrine agency is not completely ruled out. A study of autopsy material from 411 patients with coronary sclerosis show no correlation between the grade or amount of such sclerosis with the heart weight (72). The conclusion is drawn that coronary sclerosis does not bear a causal relationship to cardiac hypertrophy. In contrast to previous reports (74), no evidence of coronary artery or myocardial damage is observed following prolonged administration of massive doses of acetylcholine (73).

The time for establishment of retrograde flow in coronary arteries in the dog after ligation, has been studied (75). The volume



of flow is small for some hours and increases progressively for several days. Disturbance of normal pressure gradients in pre-existing collaterals is apparently the basis of the reverse directional flow. Increase in either venous or arterial pressure augments the retrograde flow. Studies on establishment of new collateral coronary sources by extrapleural cardio-omentopexy are also reported (76).

The mortality in dogs following ligation of the descending branch of the left coronary artery in thirty cases is reported to be 80 per cent (77). When this operation is combined with ligation of either the coronary sinus or the vena magna cordis the mortality in fifty-seven cases was 61 per cent. When partial occlusion of a coronary artery is performed a smaller area of infarction occurs when venous occlusion is performed in addition. The protective effect of venous occlusion upon the consequences of arterial obstruction is not great. Papaverine hydrochloride, in doses of 11 mg. per kg., intravenously injected prior to coronary arterial ligation reduces the mortality from this procedure in dogs from 75 to 50 per cent (78). The drug does not abolish objective evidence of cardiac pain. Studies are reported on the effect of quinidine sulfate, in doses of 32.5 mg. per kg., upon the results of coronary artery ligation in the dog (79). The death rate is only slightly reduced by the drug, but the objective evidences of pain following ligation were greatly decreased or abolished.

In forty-six cases, a rather small series, coronary disease was found to be somewhat more frequent in smokers than in non-smokers in the age range forty to fifty-nine years (80).

*Cardiac lymph.*—Cardiac lymph flow in dogs is found to increase when oxygen tension is lowered (180).

*Fetal circulation.*—The course of blood through the fetal heart has been studied in the cat and the guinea pig (81). India ink injected into the jugular veins of fetuses does not enter the left atrium through the foramen ovale. Instead it enters the right ventricle and stains the lungs. When injected into the umbilical vein the ink passes mainly through the foramen ovale into the left atrium. No staining of the lungs occurs under these circumstances. Direct evidence is thus afforded for the crossing of streams of blood in the right atrium without appreciable mixing. This situation had been inferred earlier from observations on the oxygen content of blood in various fetal vessels (181).

A working model of the crossing caval blood streams in the



fetal heart has been studied (82). When fluids of different colors are perfused via the superior and inferior vena cavae, the fluid from the latter emerges largely from the foramen ovale with very little admixture with superior vena cava fluid, provided that the perfusing pressure is 20 mm. Hg. greater in the inferior vena cava.

*Functional pathology.*—An exhaustive analysis of the simultaneous determination of cardiac output in man by the acetylene and x-ray kymograph methods is reported (84). In fifty-four normal subjects, when an empirical factor relating cardiac area change to volume change was used, the correlation between the roentgenkymograph and the acetylene values for stroke output was found to be close. It is found that the Valsalva and Müller effects do not introduce serious errors in x-ray kymography of the heart with quiet breathing. In patients with valvular insufficiency the kymograph values are larger than the acetylene figures. The discrepancy is a measure of the "leak" and is roughly proportional to the pulse pressure. Studies are reported on twenty-six patients with patent ductus arteriosus (83). Simultaneous acetylene and roentgenkymographic measurements of cardiac output show a gross ventricular output averaging 25 per cent greater by the second method.

The peripheral pulse in aortic stenosis has been analyzed (85). The systolic discharge is so altered that standing waves are not set up. In aortic insufficiency the increase in systolic arterial pressure in the lower as compared with the upper extremity is much greater than in the normal (86). The discrepancy may be as great at 100 mm. Hg.

A study of the total cardiac vibrations in one hundred normal subjects is presented (87). Attention is called especially to the low frequency waves which are presumably due to vibrations of the walls of the heart. In human subjects with severe myocardial damage low frequency vibrations are abnormally prominent in the vibrocardiogram. These changes are believed to reflect alterations in the elasticity and contractile power of the heart (88). The features of the esophageal pulse in man have been recorded with suitably placed balloons (89). Evidence is presented that in mitral stenosis the contributions of atrial contraction to ventricular filling is greater than in the normal. Pulmonary circulation time by the cyanide method has been measured in the human at several body temperatures (90). Extreme lowering of body temperature prolongs the pulmonary circulation time as much as 80 per cent.



Right ventricular hypertrophy is observed in rats after exposure for seven to twenty-one days to 80 to 85 per cent oxygen in air at normal barometric pressure (91). High grade cardiac hypertrophy in rats is produced by encapsulating both kidneys in molded gauze-collodion (92). Maximal heart changes are seen in thirty days.

Anastomosis of the right carotid artery into the external jugular vein in rabbits results in cardiac hypertrophy and dilatation (93), greater in the right than the left ventricles, and most marked in the atria. The latter may increase to four times their normal weight. The "effective refractory period," the earliest moment at which an impulse can be liberated after its predecessor and be conducted through the muscle, is within normal limits in rabbit hearts hypertrophied by arteriovenous anastomoses (94). Heart failure was produced by intrapericardial injections of various toxic materials, including the tincture of iodine and Dakin's solution (95). Systemic venous pressure elevation was regularly produced without pericardial effusion. Cardiac dilatation occurred, predominantly right ventricular. The direct or indirect effects of the agents employed upon the heart muscle are presumably responsible for the state of cardiac failure. A study of 796 necropsied cases of rheumatic heart disease shows the valves of the left heart to be involved in 99.8 per cent of cases (96). The incidence in females is slightly greater than in males, but the latter lived longer than the former, perhaps because of the greater incidence of aortic valve involvement in the male. The average age at death was higher in the aortic than in the mitral disease groups. No indication was found of a correlation between rheumatic and coronary arterial disease.

Studies of changes in finer structure of heart muscle treated with caffeine show alterations in physical alignment of the cross striations and bending of myofibrillae (97). Diphtheria toxin in dogs does not decrease the ability of the heart to meet added loads of work (98). The isolated frog heart perfused with Ringer's fluid is not affected by diphtheria toxin (99). The mercurial diuretics, salyrgan and novasurol, produce atrioventricular block in the turtle heart at concentrations of 12 to 20 mg. Hg. per 100 cc. (100). In the absence of copper, the perfused frog heart does not respond to addition of ascorbic acid (101). In the presence of 0.1 to 0.4 micromols per liter of copper, ascorbic acid has a regular effect. Observations



on cats fail to show toxic effects of relatively large doses of veritol on the heart (102).

*Age.*—A mathematical study of growth of heart fragments *in vitro* is reported (103). The influence of age upon pulsation frequency has been studied in the chick embryo heart (104). The incidence of electrocardiographic changes by age among 2,400 males has been analyzed (105).

*The excitation process and electrophysiology of the heart.*—An exhaustive comparative anatomic study has been made of the nodal and conduction systems in several ungulates, in the dog, and in man (106). The tissue described as the sinoatrial node of Keith and Flack is reported to consist of muscle fibers histologically indistinguishable from types found elsewhere in the atrium. Nerve trunks and groups of ganglion cells in the location of the node are found in the epicardium. Numerous muscular bridges are seen between atrium and ventricle in the atrioventricular groove. These observers report further that in the dog and in man they are unable to observe a characteristic Purkinje system (107). Seventeen canine and thirty-six human hearts were studied. They find a distinct Purkinje system in sheep, cattle, and swine hearts, but only vestigial remnants in the horse. Forty hearts of these groups were studied. Most earlier observations on Purkinje tissue have been made in the ungulates. The present work casts grave doubt upon the reality of the existence of a morphologically differentiated conduction system in the dog and the human. In this connection the disagreements in the literature concerning the velocity of transmission of excitation over the atrioventricular bundle as compared with ventricular muscle in the dog are of interest (108). Further physiological studies on conduction pathways in canine and primate hearts are obviously indicated to resolve the present uncertainty as to the functional significance of myocardial elements which have been interpreted by some observers to be Purkinje cells. The important physiological problem is to ascertain positively whether or not the tissues in question are functionally differentiated.

In the turtle it is found that contraction waves over the sinus venosus can be visualized by the use of high speed cinematography (109). It is observed that these waves progress radially in all directions from a small focus. This evidence confirms the existence



of a functional pacemaker. The location of the pacemaker has been studied by several methods (110), including the painting of small portions of the sinus venosus with a kaolin paste containing acetylcholine. Inhibition occurs only when the pacemaker area is covered. This area lies on the ventral surface of the sinus, anterior to the coronary vein, and to the right of the midline.

In a study of the relation of the Q-T interval to the refractory period, the heart rate, and the duration of contraction, it is shown: (a) that the Q-T interval coincides with the absolute refractory period; (b) that the Q-T interval is smaller the shorter the time between the last T wave and the shock eliciting the extra beat; and (c) that the conduction rate is higher with increased contraction frequency. The duration of contraction is found to be directly proportional to the Q-T time. Some evidence is presented to support the contention that the state of polarization of the heart muscle directly controls the release of contraction energy (111). The turtle ventricle is absolutely refractory (112) until the end of electrical systole in some portion of it. The latent period for excitation as measured electrically does not increase when stimuli are applied earlier in diastole. However, the mechanical changes are slower.

New observations show that surface injuries to the dog heart produce very much greater changes in the electrocardiogram than do injuries of comparable areas beneath the surface (113). The S-T segment is greatly altered by surface application of 0.2 M potassium chloride or calcium chloride (not by sodium or magnesium salts), while subsurface injection is nearly without effect. These observations suggest that the externally measured electrical activity of the ventricles may be a phenomenon determined largely by processes occurring at the surface of the heart.

An extension of these observations to studies of the conventional electrocardiogram in the dog, cat, and monkey after soaking the surface of either the entire right or left ventricle with 0.2 M potassium chloride has led to important results (114). When the right ventricle is so treated the electrocardiogram closely resembles the monophasic record derived from the left ventricle. The abnormal deflection in all three leads is directed downward. It is considered to reflect the electrical activity of the left ventricle. The reverse changes are found when the left ventricle surface is treated



with potassium chloride. The algebraic sum of the two curves at isochronous points gives a curve closely resembling the normal electrocardiogram. Applying the same method to a study of injury to adjacent portions of both ventricles or to one ventricle alone it is found that elevation of R-T in one lead and depression of S-T in another results from damage to contiguous areas in both ventricles. When the injury is restricted to one ventricle the RST complex is deflected in the same direction in all three conventional leads (115).

Studies of the electrocardiogram (116, 116a) in relation to local cooling or heating of portions of the heart show changes in the rate of recovery depending upon temperature; these results confirm earlier work. The P-R interval in dogs increases from 0.10 sec. at 34 to 38° C. body temperature to 0.22 sec. at 18 to 22° C. (117). The Q-T segment also increases in duration. The changes are reversible.

In decerebrate dogs exposed to oxygen at five atmospheres, bradycardia appears (118). The P-R interval is also increased as much as 40 per cent. This effect during the early period of poisoning by oxygen is abolished by vagotomy. The terminal effects in the same direction are, however, not dependent upon the vagi. The concentration of cyanide necessary to produce inhibition of sinus venosus rhythm in the frog heart increases with the oxygen tension (119).

The myoneural junctions of the heart of *Limulus polyphemus* are not affected by acetylcholine, nor by physostigmine (120). The cardiac ganglion is sensitive to these agents, but in relatively very high concentrations. The sensitivity of the denervated cat heart to epinephrine increases (121) with time after denervation to at least thirty days. The greatest increase occurs during the first five days.

The staircase phenomenon in heart muscle has been further analyzed (122). The augmentation is greatest when conditioning stimuli are thrown in during the relatively refractory period producing weak contractions. Then after a suitable delay, a second stimulus results in a contraction showing maximal augmentation.

Exposing human subjects to 20,000 feet equivalent altitude in a decompression chamber breathing air produces a slight and inconstant lowering of the T wave (123). Exposure to 30,000 feet breathing oxygen is without effect on the E.K.G. Another investigation shows a decrease in T. voltage when the subject is at 15,000



ft. for two hours (124). Elevation of T voltage is seen (125) in a majority of cardiac patients when they are given pure oxygen. An extensive clinical study of the significance of the momentary electrical axes during the cardiac cycle has been reported (126). Changes in the electrocardiogram associated with the distention of the stomach in man are described (127).

By analysis of electrocardiograms, phonocardiograms, and pulse records the asynchronism of right and left ventricular contraction in ventricular extrasystole can be studied (128). Premature beats with negative deflection in lead I are associated with earlier left ventricular ejection as judged by central arterial pulse measurements than are beats with positive deflections in that lead.

It has been found in one hundred consecutive cases of bundle branch block in man that the heart was enlarged in all subjects examined *post mortem* (129). Diffuse myocardial damage was found in each instance. The type of bundle branch block was dependent upon which ventricle was enlarged rather than upon extent of damage in either or both ventricles. These results have a bearing upon the anatomical studies of the conduction system mentioned previously. A careful study has been made of the characteristics of the chest lead electrocardiograms of one hundred normal adults of both sexes (130). These measurements provide useful normal standards and indicate which of the several suggested chest leads may provide the greatest amount of diagnostically significant information.

*Ventricular fibrillation.*—A new series of observations has been made on the genesis and methods of interruption of ventricular fibrillation. Ventricular fibrillation is described as occurring in four stages (131). The first or undulatory stage may represent a series of incomplete ventricular extrasystoles, or a single premature contraction with re-entry into portions of the heart muscle which have passed the refractory phase. The second stage is characterized by more frequent waves which the author designates as the period of convulsive incoordination. In the third stage progressively smaller areas are involved in fibrillary contraction, while in the fourth stage large regions are quiescent and toward the end only the region overlying the ventricular septum shows slow waves of contraction. The theory that fibrillation results from the formation of circuits limited by blocks due to one or another cause, with re-entry of impulses after the termination of the refractory phase, is



supported. It is necessary to emphasize particularly the three dimensional character of impulse fronts.

The physiological principles underlying practicable methods for resuscitation from ventricular fibrillation are discussed (132). It is pointed out that defibrillation can be accomplished only if the natural pacemakers survive and the entire ventricular myocardium is made quiescent. A new technique of serial application of alternating current shocks is described which has been found to be highly successful in defibrillating exposed hearts. It is pointed out that electric shock therapy is not adapted to use in man without exposure of the heart because of the high voltage and amperage necessary for attainment of defibrillation.

A new quantitative measure for the "fibrillation threshold" of the ventricles has been introduced (133, 133a). It consists in measuring the current strength of brief direct current shocks of constant duration which are just able to set up fibrillation when applied during late systole, the vulnerable period, to a given region of heart surface. This threshold is constant over several hours despite repeated fibrillation and defibrillation. The duration of the vulnerable period is greater when contraction is idioventricular (134). Procaine hydrochloride (10 mg. per kg.) raises the fibrillation threshold. Very high concentrations of papaverine in the coronary perfusion fluid have been found to abolish an existing ventricular fibrillation with restoration of coordinated contractions (135). The fibrillation threshold of the dog heart is very considerably increased by administration of papaverine. Vagal stimulation was found to be ineffective in abolishing ventricular fibrillation in seventy-eight dogs (136). Brief coronary occlusion consistently lowers the threshold (137). Since anoxia also favors the setting up of ectopic foci the tendency to fibrillation in coronary occlusion may probably be looked upon as the result of coincidence of these two changes.

Studies of ventricular fibrillation occurring after administration of toxic doses of digitalis or ouabain show that the "fibrillation threshold" to direct current shock is not altered by these drugs (138). Apparently the drugs themselves produce the condition of local blocks necessary for the occurrence of fibrillation. These observations underscore the point that the conditions causing ventricular fibrillation are not always the same and that therefore each set of circumstances must be considered separately.



Fibrillation can be produced by either cathodal or anodal polarization of a portion of ventricular surface, the indifferent electrode being inserted in the body wall (139). Polarizing currents insufficient to induce full fledged contractions produce undulations in the electrogram in rapid cycles. Stronger currents induce a tachycardia which may terminate in fibrillation. In another study it has been found that application of brief direct current shocks of from 1 to 40 volts during the vulnerable period of the cardiac cycle produces a series of focal discharges, apparently arising from the same focus, as judged by the character of the electrograms recorded (140). These repetitive discharges may occur at 60 msec. intervals. It is suggested that fibrillation may begin with a series of ectopic beats from a single focus. The observation that the absolute refractory period of heart muscle is smaller the shorter the interval between contractions is pertinent in connection with these phenomena (111).

*Nervous and chemical control.*—A cardioinhibitory substance appearing in blood or other media perfusing the brain of the dog has been noted (141). The substance is not adenylic acid, it is heat stable, and is soluble in acetone, alcohol, and water. This substance appears to contribute to the chemical regulation of the heart rate in the heart-lung-brain preparation and may be of importance to the intact animal. Physiological salt solutions perfused through frog hearts by means of a Straub cannula, accumulate a cardioinhibitor substance in the absence of vagus stimulation (142). The action of this substance is abolished by atropine. It is deduced that such frog hearts normally liberate choline ester-like substances, independently of vagal stimulation.

Increasing the intracranial pressure in cats under ether followed by chloralose causes cardiac slowing, whether or not the blood pressure rise is prevented (143). Peripheral pressure receptors are therefore not responsible for this action. The presence, in the cardioaortic zone, of receptors sensitive to variations of osmotic pressure has been studied (144).

Stimulation of the preoptic region in cats produces a cardiac slowing which is reduced but not abolished by bilateral vagotomy (145). Hypothalamic stimulation results in acceleration, which is diminished but not eliminated by adrenalectomy. A further study has been made of the so-called Bezold effect (146). Intracardiac receptors are apparently stimulated by veratrine and other agents.



Denervation of the ventricles abolishes certain of their effects. Studies on the dog show that when the left vagus is intact the injection of pitressin or neosynephrine frequently produces heart block. With the left vagus cut and the right intact, sinus bradycardia occurred without heart block. The reflex slowing occurs via either vagus, but only the left vagus exerts sufficient effect on atrioventricular conduction to produce block (147). Studies are reported on the influence of local narcosis of the vagus nerve on cardiac reflexes (148).

After a decline in the denervated heart rate, intravenous injection of acetylcholine produces a considerable increase in the heart rate, both in dogs with normal adrenals and after demedullation (149). The effect is less in the latter case. A comparable rise in the denervated heart rate follows injection of nitroglycerin. Acetylcholine and nitroglycerin have a hypotensive action in common. It is inferred that even in the absence of adrenal medulla, sufficient epinephrine (sympathin) is liberated at pressor reflex nerve endings to have a marked humoral effect.

The actions of acetylcholine on the cat and dog heart have been studied with the aid of a combined piezoelectric manometer and intracardiac electrode (150). The authors state that acetylcholine causes a reduction in diastolic as well as systolic intraventricular pressure, but unfortunately they provide no calibration for their records, and it is impossible to evaluate their data properly. Studies are reported on the relative importance of cardiac and peripheral vascular actions in the effect of acetylcholine, epinephrine, and histamine upon the blood pressure (151, 152, 153). The direct cardiac effect is stressed. Administration of 1.0 mg. atropine sulfate to two normal humans resulted in an average increase in cardiac minute volume of 21 per cent in twelve trials (154). The heart rate increases from 16 to 50 per cent in the several trials.

The addition of 1 mg. choline per cc. of perfusion fluid decreases the response to acetylcholine and vagus stimulation in the frog heart (155). Cat, rat, and guinea pig hearts perfused by the Langendorff method show (156) a decreased response to epinephrine and to sympathetic nerve stimulation after treatment with piperidinemethylbenzodioxanes (933F). The bradycardia and hypotension resulting from intravenous injection of whole bile or bile salts in the dog are obtained after presumably complete denervation of the heart (157). The production of ventricular tachycardia



by epinephrine in cyclopropane anesthesia has been given attention (158).

The effects of excitation of the cardiac nerve on the automaticity of the heart of *Helix pomatia* are described (159). A decrease in ventricular tonus and a temporary cessation of contraction are observed upon such stimulation. The innervation of the supracardial bodies in the cat has been investigated (160).

Studies of the electrocardiogram in the human during insulin shock therapy are presented (161). Variable alterations particularly in the QRS complex are noted. A study has been made of disturbances in cardiac contraction in the diabetic state (162). Reflections of disturbed muscle metabolism are evident in prolonged systole and other changes. Tobacco smoke and nicotine produce directionally similar changes in blood pressure and limb volume in dogs (163).

*Heart sounds.*—By immobilizing the atrioventricular valves, either by ligature or by inflated balloons, new studies were made of the muscular component of the first heart sound (164). As long as contraction is vigorous, the first heart sound is audible regardless of the method employed for immobilization of the valves. It is observed that in myocardial infarction, due to acute coronary occlusion, there is an increased incidence of atrial and third sounds (165). The first heart sound is usually diminished in amplitude and of low pitch. A theoretical and experimental study of auscultation has been reported; a description of amplifying and recording apparatus is included (166). The importance of various factors such as chest piece diameter, tubing length, air volume, filtering action of skin tension, artificial filters, etc., is considered in detail.

*Methods of investigation.*—An amplifying and recording device is described for study of heart sounds and lower frequency vibrations in the human (167). A sound filter technique for phonocardiography is described (168) and its advantages discussed. A new type of membrane for direct phonocardiography is presented (169). An electrostethophone and recording apparatus for fetal and adult heart sounds has been described (170).

A piezoelectric manometer is described and applied to the recording of intracardiac pressures (171). The advantage claimed for the arrangement is mainly its convenience. The cannula is constructed from silver and is insulated except at its tip. It can therefore be used as an intracardiac lead in recording electrograms,



an indifferent electrode being placed on some other part of the animal's body.

Methods for visualization of the chambers of the heart and the great vessels in man are outlined (172). A modified technique is presented for timing x-ray kymograms and instantaneous exposures in relation to the cardiac cycle (173).

A right-atrium preparation for studying pacemaker activity and the amplitude of contraction is described (174).

Catheterization of the right atrium has been performed in man (175) and blood samples taken for analyses. The cardiac output is calculated from arteriovenous oxygen and carbon dioxide differences, and the total gas exchange.

An analysis, by means of hydraulic models, of the factors operating to produce the typical ballistocardiogram shows that it is the rate at which the velocity of ejection increases rather than the stroke volume output that determines the size of the initial deflection (176). Studies on the human show that the ballistocardiographic waves are related to the periodic surges in the aortic "Windkessel" (177).

Studies of oxygen debt and total ventilation with standard exercise in normal subjects and in persons with cardiac disease indicate that these measures are useful indices of reserve capacity (178). The importance of the condition of the lungs to the results of such measurements is pointed out. A method for estimation by the foreign-gas method of the net (systemic) cardiac output in conditions where there is recirculation through the lungs is outlined (179).



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DEPARTMENT OF PHYSIOLOGY  
UNIVERSITY OF MINNESOTA  
MINNEAPOLIS, MINNESOTA



## BLOOD

BY H. P. SMITH

*Department of Pathology, State University of Iowa,  
Iowa City, Iowa*

In planning this review the author found it necessary to neglect important aspects of the subject. Blood coagulation was given detailed consideration because recent progress has been rapid, and widespread interest has been aroused. This subject was omitted from last year's review; the present review, therefore, covers the two year period ending June 30, 1941. The source, production, and utilization of plasma proteins has been reviewed elsewhere (1). For these reasons they are given only incidental mention here. In the discussion of cellular elements, consideration is given mainly to the formation of erythrocytes. Problems of sedimentation are covered in an extensive report by Bergenheim (2).

### THE COAGULATION OF BLOOD

The literature of blood clotting has been the subject of several reviews (3 to 7).

*The role of calcium.*—Larson (8) stresses the value of sodium hexametaphosphate as a decalcifying anticoagulant. Quick (9) found that the anticoagulating effect of oxalate is not immediate, and he believes that the calcium concerned in clotting pre-exists in nonionized form, apparently in combination with prothrombin itself.

Mellanby & Pratt (10) believe that the rate at which thrombin is formed by thromboplastin is increased by calcium, but that the latter is not essential to the reaction; nor is calcium thought to be a part of the thrombin molecule.

*Fibrinogen and fibrin.*—Ebbecke (11) studied the physical chemistry of fibrin formation. Studies on turbidity and Tyndall effect during clotting are also reported (12), as is the use of the electron microscope (13). Clark (14) reported that fibrinogen and thrombin are levorotatory. When the two are mixed, a dextro-rotatory compound is formed, but as the clot begins to form, there is a change to levorotation, due, it is thought, to structural asymmetry in the gel.



Glanzmann *et al.* (15) reported cases of fibrinogen deficiency in childhood. Fanconi (16) believes that the fibrin found in certain patients is abnormal ("fibrinasthenia"), but controlled studies are lacking. It has been reported (17, 18) both in man and in animal experiments that hypertension may bear some relationship to increased fibrinogen content of the plasma.

*Thromboplastin.*—Thromboplastic activity is possessed by cephalin, and also by certain cephalin-protein compounds. Chargaff *et al.* (19, 20) have recently made efforts to isolate the latter from beef lung. The behavior of the compound in the electric field at various pH levels indicated a rather firm type of union. They showed that the compound is not readily dissociated by organic solvents, but can be made to dissociate by addition of heparin, or even by prolonged shaking. As shown originally by Mills, the protein component, after removal of the phosphatides, is devoid of thromboplastic activity. Chargaff & Ziff (21) also reported studies on the ability of basic proteins to combine with cephalin. Salmine and thymus histone were particularly effective; globin was not. In these artificial compounds the cephalin no longer possesses its thromboplastic activity. Chargaff & Cohen (22) also studied the inactivation of cephalin by certain snake venoms. The lysocephalin resulting from the interaction is inactive, presumably because of the loss of unsaturated fatty acids. Cohen & Chargaff (23) made a study of the products resulting from hydrolysis of the lipoid fraction of the thromboplastic protein of lung.

Michimoto (24) stresses the fact that the active cephalins are highly unsaturated. These compounds are said to be much more abundant in blood vessels and in heart than in other organs.

Palmer *et al.* (25) presented x-ray diffraction studies on lipoproteins and found patterns which correspond to the analytical data on combining proportions.

Glazko & Greenberg (26) reported concerning a dialyzable, organic, heat-labile factor in plasma which acted as a thromboplastin in accelerating coagulation. Ferguson & Erickson (27) have presented further data regarding a hypothetical protease ("thromboplastic enzyme") which is thought to liberate phosphatides and calcium from their union with proteins, thus making them more readily available for the clotting process. Crystalline trypsin was thought to accelerate clotting through action of this type. Rather indefinite is the report of Grunke (28) that urine contains a clot-



accelerating factor. This factor is scanty in liver disease and in certain of the blood dyscrasias.

Rix & Ehrhardt (29) found that carbon dioxide strengthens the thromboplastic powers of tissue extract. The effect of altered pH was not carefully studied, however. They found that oxygen has a prompt deleterious effect on thromboplastin. Mechanical agitation does the same, but this alteration is said to be reversible on standing. Quastel & Racker (30) found that tissues extracted anaerobically yielded more potent thromboplastin than when extracted aerobically.

Winternitz *et al.* (31) made extended observations on the effects of intravenous injection of tissue extracts.

Oxalic acid has been suggested as a means of shortening the coagulation time. Its supposed action may be concerned with the liberation of thromboplastin. A number of papers have appeared (32 to 39).

Calder & Kerby (40) found that nicotinic acid accelerates blood clotting *in vitro*, but Aggeler & Lucia (41) report that the effect is due merely to cytolysis of cells and platelets with liberation of thromboplastin. That this may not represent the only mechanism is evident from the fact (40) that nicotinic acid, given orally, is effective under some circumstances.

*Prothrombin and thrombin: assay procedures.*—Various assay methods agree under some circumstances, but not under all. Warner *et al.* (42) have presented evidence to show that in the one-stage prothrombin methods, the prothrombin conversion rate, and hence the "prothrombin time" may vary despite the addition of an "excess" of thromboplastin. They believe that the two-stage methods avoid this pitfall, for time is given for complete conversion of the prothrombin, after which the thrombin titer is ascertained. Herbert (43) has made extensive studies and, after introducing a few modifications, has expressed approval of the two-stage technic. Ferguson & Glazko (44) have also given qualified approval to the two-stage principle. They believe, however, that inhibitors interfere seriously with the prothrombin conversion in all methods, but especially with the one-stage techniques. Quick is the most consistent critic of the two-stage procedure. In his most recent article (45) he outlines certain features which he considers objectionable in the two-stage methods. It is evident, however, that much speculation is involved and it must be agreed that new methods of ap-



proach must be found to solve these problems to the satisfaction of all concerned.

The one-stage technique devised several years ago by Dam and his associates gives extremely low values in cases of prothrombin deficiency. The reasons are not yet apparent. The clot retraction test has received further study (46) as an index of prothrombin deficiency. The one-stage method of Quick has received much study (47 to 54) and some modifications. Viper venom has been used (55, 56, 57) in the test as a source of thromboplastin. There has been widespread insistence on preliminary dilution of the plasma in order to detect minor degrees of prothrombin deficiency. The one-stage method of Quick has also been simplified (58) to permit use of whole blood instead of plasma ("bedside test"). Several micro adaptations (59 to 75) of one-stage procedure permit analysis of blood obtained from stab wounds—a great advantage in the study of infants or of small animals.

Thromboplastin in dried form<sup>1</sup> has been placed on the market for use with various one-stage prothrombin tests. Imidazole buffer does not eliminate the calcium ion from solution and is very valuable (76) for many types of study on blood coagulation.

*Prothrombin and thrombin: purification and properties.*—Seegers (77) has improved the technique of producing purified prothrombin and thrombin. The potency was such that 1 mg. of thrombin would cause clotting of 950 cc. of purified fibrinogen in fifteen seconds. He reported that at the isoelectric point thrombin is much less soluble than prothrombin, this fact indicating that prothrombin undergoes important physicochemical changes on being converted into thrombin. Heat inactivation curves were also given. Analyses showed high carbohydrate content of both the prothrombin and the thrombin preparations.

Astrup & Darling (78) prepared thrombin having a potency of 10 units per mg. Later, they (79) isolated a fraction having a potency of about 100 units per mg. (603 units per mg. nitrogen). The product contained less than 0.1 per cent phosphorus. Tests with ammonium sulfate indicated that thrombin is an albumin. However, the product is only 20 per cent as potent as that of Seegers, and even the latter is probably impure. Both from this

<sup>1</sup> The Abbott Company, North Chicago, has prepared dried lung. E. R. Squibb and Difco Laboratories have prepared a lipoid type of thromboplastin which is almost as suitable for the "bedside test."



work and from that of Seegers it is evident that satisfactory chemical characterization must await the isolation of thrombin which can be shown to approximate complete purity.

Orr & Moore (80) agree that prothrombin is precipitated from plasma along with the globulins, but, like Astrup & Darling, they report that electrophoresis studies show that it migrates with the albumins.

Scheuring (81) has reviewed the theory of Bordet that in the process of clotting prothrombin is formed from an inactive precursor. He concludes that this view rests on insufficient evidence.

Warner *et al.* (82) and Andersen (83) report concerning the use of purified thrombin as a hemostatic agent. Parfentjev (84) describes a thrombin preparation which may serve similar purposes.

Recent evidence (85) tends to favor the view that spontaneous fibrinolysis is due, not to thrombin, but to some coexisting proteolytic enzyme. If so, both enzymes are affected in a similar manner by a number of inhibitors (86). Glueck & Mirsky (87) believe that the incoagulability of menstrual blood is due to fibrinolysis, not to faulty clotting.

Dyckerhoff & Gigante (88) report that the ability of commercial papain to cause clotting is due, not to papain, but to contamination with a thrombin-like material ("phyto-thrombin").

*The conversion of prothrombin into thrombin.*—Dyckerhoff (89) believes that thrombin is fully formed in blood, but is masked by inhibitors which can be eliminated in a variety of ways, including the use of thromboplastin. Wöhlisch (90) adheres strenuously to the enzymatic nature of "thrombokinase." As with other enzymes, the activity is proportional to the amount of kinase present. However such proportionality is also true of many nonenzymatic chemical reactions. It might be added that thromboplastin is definitely consumed in the reaction. Thus, Mertz *et al.* (91) found that the prothrombin and thromboplastin react according to simple laws of stoichiometry. They also found that in high concentration, thrombin causes inactivation of its own precursor, prothrombin. Ferguson (92) has questioned these conclusions, though obviously the preparations used in his studies were less potent.

According to Mertz *et al.* (91) very little thromboplastin is consumed in the conversion of prothrombin into thrombin (1 part or less to 250 parts of prothrombin). Whether the thrombin is formed by simple union of prothrombin and thromboplastin or



whether cleavage phenomena occur is not known. Chergaff & Ziff (93) used thromboplastin containing radioactive phosphorus and found that the thrombin prepared with its aid contained very little if any of the radioactive material. This is in accord with data (79) showing that purified thrombin contains little or no phosphorus.

Astrup (94) states that conversion is autocatalytic in native plasma, but not with purified reagents. The latter corresponds to the experience of Mertz (91, 95) and of Ferguson (92).

Astrup (96) makes further study of the "inoculation" experiment of Fisher and finds the clotting curve is like that of autocatalysis, but controls show the falsity of this concept. He does not know why the phenomenon occurs.

*The formation and utilization of prothrombin.*—Evidence, too voluminous to quote in its entirety, continues to mount that the liver is vitally concerned in the manufacture of prothrombin. The plasma prothrombin level falls markedly following hepatectomy (97, 98). A transitory fall can even be produced by mechanical trauma to the liver (99, 100). Wilson & Doan (101, 102) found a marked fall in certain cases of induced fever therapy, a result of liver injury. In various clinical conditions, Wilson (103) also reported good correlation between the prothrombin level and the hippuric acid test for liver function. It is assumed, of course that vitamin-K deficiency is first excluded by means of the therapeutic test. Two other reports (104, 105) fail to confirm the correlation with liver function in borderline cases, but it is, perhaps, significant that they employed a one-stage prothrombin technic rather than the two-stage technic employed by Wilson. Lord (106) found that the prothrombin level is depressed in hyperthyroidism, because of impaired liver function in this disease.

Brinkhous & Walker (107) reported that prothrombin occurs in large amounts in the lymph which drains from the liver, but to a less extent in lymph from other portions of the body. This observation may be associated with the hepatic origin of the prothrombin, but it may, instead, be due to the greater tendency of blood colloids to pass from the hepatic capillaries into the lymph.

Andrus *et al.* (108) presented evidence that prothrombin is destroyed in large quantities in the lungs. Tocantins (109) produced reduction of the prothrombin level by the injection of immune serum. Shafiroff (110) found that the intravenous injection



of sodium citrate causes an increase in the plasma prothrombin level. This is denied in another report (111). Tocantins & O'Neill (112) report that intravenous injection of epinephrine causes increase in the one-stage prothrombin level.

*Prothrombin and vitamin K: general considerations.*—The isolation of vitamin K and its chemistry have been reviewed elsewhere (3, 4, 5, 113 to 119). Certain of the synthetic vitamin-K analogues are water soluble. Unlike vitamin K<sub>1</sub> and K<sub>2</sub>, they are readily absorbed even though bile is excluded from the intestine (120, 121, 122, 123)—an advantage in human therapy, since bile salts tend to be nauseating. Elliott *et al.* (124) showed that mineral oil interferes with the absorption of fat-soluble K from the intestine, a finding which agrees with reports (125) regarding the administration of vitamin K in oily mediums. Almquist (126) reported that activated carbon interferes with the absorption of vitamin K, and Ansbacher (127, 128) found that when chicks were given a special heat-treated diet, very little vitamin K was formed by intestinal bacteria, thus minimizing the danger of coprophagy and refec-tion.

Vitamin K is known to be concerned in the production of prothrombin, but the mechanism by which it does so is still obscure. Most of the compounds described are naphthoquinones, though at least one is a benzoquinone (129). The biological activity of the latter is very slight, however. Certain of the anthraquinones are inactive (130, 131) though one of them, 1,2,4-trihydroxyanthraquinone, does have some activity (1/100 to 1/1000 as active as vitamin K<sub>1</sub>). It is significant that all of the compounds having biological activity are either quinones, hydroquinones, or rather simple derivatives of these compounds. It has been suggested (132) that vitamin K may insure the presence of the -S-S- group in the thrombin molecule, and Baumberger (133) has proposed the hypothesis that thrombin oxidizes -SH groups of fibrinogen, thereby, converting fibrinogen into fibrin. It is not yet established, however, that the prothrombin molecule contains the chemical groups which characterize the vitamin K molecule. It is entirely possible that the vitamin merely helps to maintain the prothrombin forming tissues in a productive state. However, it is perhaps significant that the processes of oxidation and reduction have a definite effect (134) upon blood clotting.

In the belief that further progress in prothrombin metabolism



requires extension of quantitative viewpoints, Tidrick *et al.* (135) have made detailed studies of the rate at which the prothrombin level falls in K-deficient chicks, of the rate of recovery on supplying vitamin K, and of problems of vitamin-K storage. Vitamin K, injected into the egg of the chick, is carried over and stored in the newly hatched chick (136). The dosage required for storage is far greater than the mere maintenance dose, both in the chick (136) and in the rat (137). Data have also been published (138) regarding storage in man. The work of Sells *et al.* (74) indicates the degree of storage possible in the human infant.

In cases of biliary obstruction, the prothrombin often falls to dangerously low levels after operation (139 to 146) despite the use of vitamin K to build up the prothrombin level prior to operation. The various workers have been unable to agree as to whether the liver is injured by manipulation (99, 100) and by anesthetic (147) or whether there is excess utilization of prothrombin in forming fibrin exudate, or whether faulty storage and scanty postoperative diet are to blame. Attempts to administer the vitamin by the oral route are handicapped by the marked tendency of the patient to vomit at this time. Fortunately, certain of the water-soluble analogues of vitamin K can be given by the intravenous route, thus permitting (121) this problem to be solved in a very gratifying manner.

Although vitamin-K deficiency is readily produced in chicks by use of deficient diets, it is difficult, though possible, to do so in the case of mammals. Cases of simple dietary deficiency in man are not entirely substantiated. Nevertheless, many patients with mild chronic disorders (148) have a moderate reduction in prothrombin, which cannot be remedied by administration of vitamin K, and in many there is no evidence of hepatic disease. It would appear that organ defects or a nutritional deficiency of unknown nature must be involved. In chronic tuberculosis there is often some prothrombin deficiency and results of vitamin-K therapy are variable (149 to 154). In addition, protracted diarrhea (141, 155, 156), steatorrhea (139, 141, 155, 157 to 162), intestinal fistulas (155, 163) and intestinal infections may interfere with absorption of vitamin K sufficiently to cause marked hypoprothrombinemia.

*Prothrombin levels in the new born.*—Almost all of the work has been in connection with the human infant, though new born animals have also received some study (164). It is now agreed that the



prothrombin level of the infant is sometimes dangerously low at birth (67, 164 to 180). The prothrombin level in the mother is thought by most workers to be normal, but some have found it to be high (178, 181) and some have found it to be low (167). The difference between one-stage and two-stage methods is striking and the problem of a convertibility factor is of great importance (182). Both maternal and fetal levels vary, and the apparent lack of correlation between the two has led to the conclusion that the two levels are built up independently. Any unusual deficiency in either level can usually be rectified by the administration of vitamin K to the mother (70, 167, 168, 179, 183, 184, 185, 186). Most workers believe that this indicates that the diet of the mother is often deficient in vitamin K, and that the prothrombin level may therefore be low in the mother or in the fetus, but particularly in the latter. However, Fitzgerald & Webster (187) believe that the use of sedatives is also a factor in some cases. Javert (173) stresses the importance of toxemia and syphilis. It is the consensus, however, that vitamin-K deficiency is a factor of major importance. Plum (178) believes that vitamin K does not pass readily through the placenta, but others (186) deny this. In any case the diet of the mother is admitted to be important. Waddell & Guerry (183) have shown that in their series the prothrombin level of the infant tends to be much higher in summer than in winter, apparently because the summer diet contains more green vegetables, and therefore more vitamin K. The variability in birth levels reported from one clinic to another is probably due largely to differences in the maternal diet in different localities and at different seasons of the year.

Even when a safe prothrombin level exists in the infant at time of birth, there typically occurs a marked decline during the first few days of life (60, 67, 70, 73, 166, 170, 171, 179, 182, 186, 188 to 195) thus creating a genuine danger of hemorrhage in almost any portion of the body. It has been suggested (196) that the liver of the newborn, being immature, is especially prone to fail in its role of manufacturing prothrombin. Be this as it may, it is nevertheless evident that dietary factors are of great importance, for the postnatal fall can be minimized or prevented by administration of vitamin K to the infant at birth (67, 166, 179, 193, 194, 195, 197). Most workers (67, 70, 170, 179, 186, 191, 194, 197, 198) but not all (199) find that the postnatal fall can also be prevented by



administering enough of the vitamin to the mother to permit storage in the tissues of the fetus.

In case the prothrombin level does fall, a rise typically occurs at about the time that the supply of breast milk becomes abundant and the infant begins to nurse effectively. The importance of the infant's diet was further emphasized by Salomonsen (191, 200, 201) who found that by giving as little as 60 cc. of cow's milk to the infant daily the prothrombin could be kept at safe levels. Milk was already known to contain very little vitamin K, and it was therefore assumed that the intake of food served merely to introduce vitamin-K-forming bacteria (188), or that the milk itself served as a medium for the growth of such bacteria (191). However, doubt has recently been cast upon the hypothesis that bacterial formation of the vitamin is essential. Through carefully controlled experiments, Sells *et al.* (74) demonstrated that the daily vitamin-K requirement of the newborn infant is only 1 to 2  $\mu\text{g.}$ , whereas some workers have thought that 1 to 2 mg. or even 5 to 10 mg. (193) are needed. After revising these figures drastically downward, Sells *et al.* were able to show that a diet of milk contains enough preformed vitamin K to meet the reduced requirements of 1 to 2  $\mu\text{g.}$  daily. In attempts to correlate the apparent discrepancies regarding the vitamin-K requirements of the infant, one should not lose sight of the fact that this vitamin may affect the convertibility factor as well as the prothrombin content of the plasma.

Until recently, most workers had assumed that birth trauma is solely responsible for the intracranial hemorrhage which is seen so commonly in the newborn infant. In view of the facts already outlined, it has been suggested that prothrombin deficiency may also be important—a conclusion which is supported by the few statistical studies which have been made (70, 175, 183, 185, 202). It seems highly probable that when the prothrombin level falls on the second or third day of life, bleeding may occur from small intracranial lesions which would otherwise remain quiescent. "Delayed bleeding" of this type might easily be prevented by the administration of vitamin K either to the infant or to the mother. Whether intracranial hemorrhage which occurs at the time of labor itself is often the result of prothrombin deficiency is still open to debate. Deficiency is probably of minor importance in case the mother has had a diet rich in vitamin K. Whenever the diet is poor



in this vitamin the danger does exist; the artificial enrichment of the maternal diet would seem to be indicated in such cases.

*Sweet clover disease.*—The Wisconsin workers (203 to 206) have found that the toxic material of spoiled sweet clover is 3,3'-methylenebis (4-hydroxycoumarin). When given to rabbits it causes marked reduction in the plasma prothrombin level, but the mechanism of the reduction is still obscure. Contrary to early reports, it was found (207) that alfalfa (containing vitamin K) does not protect rabbits against sweet clover disease. Butt *et al.* (208) have administered the toxic material to six human patients in doses sufficient to lower the prothrombin level and thus increase the coagulation time. No harmful effects were observed, and the authors visualize the possibility that such treatment may be feasible clinically as a substitute for heparin therapy in thrombosis.

*Snake venoms.*—In view of the complexity of the subject and the lack of agreement, reference will merely be made to a number of recent contributions (209 to 217).

*The inhibitors of blood clotting.*—In one sense, inorganic ions and certain simple organic compounds must be grouped with the more complex specific inhibitory agents. Glazko & Greenberg (218) report that anions of high valency exert their deleterious effect upon the thrombin, and cations of high valency, upon the fibrinogen. They believe that heparin, with its high degree of sulphonation, acts as an anion of high valency. Glazko & Ferguson (219, 220) reported that thrombin destruction is proportional both to the amount of thrombin and to the amount of antithrombin present. Jaques & Mustard (221) reported that sodium chloride at all levels tends to abolish the inhibitory effect of heparin.

The destruction of thrombin by heparin requires a cofactor which is present in plasma. That this factor is simply the albumin fraction of plasma was suggested three years ago by Quick. However, several workers now report (221 to 225) that crystalline serum albumin does not have this effect; one must therefore conclude merely that the cofactor is present in the albumin fraction. It is said (224), in fact, to be in the fraction which precipitates at 2.8 molar concentration of ammonium sulphate. Wöhlisch & Grüning (226) found that the albumins combine most effectively at higher temperatures. They also found an optimum concentration of albumin for thrombin inactivation.

Howell originally concluded that heparin has a direct inhibi-



tory action on the first phase of clotting ("anti-prothrombic"). Brinkhous *et al.* (227) have shown that plasma contains a first-phase cofactor which is essential for this effect. This conclusion was confirmed by Astrup (228). Ferguson (225) was at first critical of this concept, but in recent papers he (229) admits the existence of this cofactor; however, he still contends that heparin does have some ability to inhibit the first phase independently of the cofactor. It is difficult, however, to be certain that this minor effect is not due to traces of cofactor present as impurity in the mixtures studied.

There is no evidence to indicate whether or not the heparin cofactor for the first stage of clotting is identical with the cofactor for the second stage.

Astrup & Astrup (230) employed empirical formulae, and found that some inhibitors, e.g., heparin, form dissociable compounds when added to mixtures of plasma and thromboplastin. Recognizing the complexity of these mixtures, they refrained from drawing specific conclusions regarding mechanism. Astrup & Darling (231) state that they have isolated from plasma a co inhibitor which acts with heparin to form an antithrombin. It differs from the natural antithrombin of plasma in forming a dissociable compound with thrombin. The data on which these conclusions are based are not given, as this was a preliminary report. Bergenheim (2) found an antithrombin factor which is perhaps identical with a factor which inhibits the sedimentation of red cells.

Chargaff and his associates (19) have made a study of the effect of heparin upon the two known types of thromboplastin, i.e., cephalin and the cephalin-protein compound. They doubt the ability of heparin to unite directly with cephalin, but they present evidence to show that heparin does unite with the protein portion of the cephalin-protein compound, thus causing dissociation of the latter. The heparin-protein compound thus formed was found to retain its ability to destroy thrombin, provided the cofactor already mentioned is present. No studies were made by these authors in regard to the ability of the heparin-protein compound to block the first stage of clotting, i.e., the formation of thrombin. Presumably, the dissociation of the cephalin-protein compound, with the liberation of cephalin, would not destroy the thromboplastin activity altogether, but there is still no adequate evidence regarding the extent to which the activity would decrease.



Many details concerning heparin, and particularly its chemistry and pharmacology, are given in reviews (232, 233). Charles & Todd (234) found the crystalline heparin isolated from the various organs of any one species to be identical. Jaques *et al.* (235, 236) found that heparin isolated from different species differs markedly in potency, but not in crystal form or in sulphur content. The liver was found (237) to contain an enzyme, "heparinase," capable of destroying the activity of heparin. An "anti-heparin" has also been found in the liver by Jeney & Vályi-Nagy (238). Following intravenous injection, as much as 10.35 per cent of the heparin is excreted (239) into the urine in two hours.

Assay procedures for heparin are still not suitable for use in complex biological mixtures. Little is known about the physiological fluctuations of inhibitors. Only recently have there been any clear concepts concerning the classification of inhibitors, and very little effort has been made to conduct separate assay for heparin, and for each of the heparin cofactors. Wilson (240) has recently made a beginning in the direction of titration, but much remains to be done.

Dyckerhoff & Ruhl (241) believe that the "antithrombin" level increases in animals sensitized by the injection of foreign proteins. Lozner *et al.* (242) reported a case with prolonged clotting time, due apparently, to excess "antithrombin," though not to the heparin component. In using heparin clinically for the treatment of thrombosis, it has been observed that some patients require much more heparin than others in order to maintain a uniform prolongation of the clotting time. There have been suggestions, but without proof, that the amount of heparin cofactor may vary markedly from one patient to another. It is equally possible, of course, that the rate of elimination or the rate of destruction of heparin may vary from one individual to another.

Országh & Alföldy (243) confirmed older observations that rabbits can be "immunized" to hirudin. On injecting the "immune" serum into normal rabbits, the clotting time of blood from the latter is markedly accelerated. Copley *et al.* (244) found that injections of heparin have much more effect upon the coagulation time than upon the bleeding time.

The use of heparin to decrease the coagulability of the circulating blood in cases of actual or threatened thrombosis has been the subject of many new reports (245 to 257). Especially promising



are the reports dealing with vascular surgery. Evidence indicates that even where thrombosis has made its appearance, the use of heparin may check the process and permit organization and resorption of the thrombus.

Heparin has also been used, sometimes in conjunction with chemotherapy, to check the growth of vegetations on heart valves [literature by Fletcher (258)]. The results are not very encouraging, for the treatment appears to increase the tendency to bleed at the site of the infarcts which may develop anywhere in the body.

Jorpes *et al.* (259) acted on the older observation of Chargaff & Olson that protamine neutralizes the effect of heparin. They found that when an excess of heparin had been given to patients, the clotting ability of the blood could be restored to safe levels by the intravenous injection of protamine.

*The blood platelets.*—Poli (260) found that asphyxia causes a rise in the platelet count. Splenic contraction is partly responsible. Solandt & Best (261) made additional studies on the power of heparin to prevent the platelet agglutination which is so important in the formation of white thrombi. They reported that the inhibitory effect was not immediately manifest. The dose of heparin necessary to prevent formation of platelet thrombi within vessels is much less than that needed to prevent the process in a glass cell. Rose & Boyer (262) confirmed the work of Trolandt & Lee that in thrombocytopenic purpura a substance can be extracted from the spleen which depresses the platelet count in rabbits. Hobson & Witts (263) found the effect only where large doses were injected. Three other reports (264, 265, 266) were entirely negative.

Hirschboeck (267) found that blood clots even more slowly in a collodion-lined tube than in a paraffin-lined tube. This is probably related to platelet stability, but it is surprising in view of the fact that water adheres to collodion almost as firmly as to glass. Studies with "lucite" vessels were also made (268). Fonio (269) has described the disintegration of platelets as viewed in the dark-field microscope. Wolpers & Ruska (270) made studies with the electron microscope. Rabinowitz (271) believes that faulty clot retraction in thrombocytopenic purpura is due not merely to lack of platelets, but is the result of a failure of oxidation-reduction functions performed by the liver. They find the iodine number of the fatty acids of the blood to be low, and they believe that a dis-



turbance in cysteine, cystine, and methionine occurs. The administration of the latter compound gave relief to patients.

*Hemophilia.*—Bendien & van Creveld (272) report regarding the coagulation globulin which they believe to be lacking in this disease. They do not believe it to be a thromboplastin, but think it is concerned in some manner with the activity of prothrombin. Ferguson (273) believes the missing factor to be the "thromboplastic enzyme factor" previously described by him. Lozner *et al.* (274), like Howell (275), report that the unknown factor can be obtained in potent form, free of prothrombin and fibrinogen. Clinical tests with the material are reported (274, 276).

The work cited does not eliminate the possibility that the factor is thromboplastic in nature. Dam (277) reported that rather large quantities of thromboplastin are needed to correct the deficiency and Howell (275) finds the missing "plasma thromboplastin" to be nonprotein in character. Brinkhous (278) showed that the platelets disintegrate slowly in hemophilia, thus liberating the thromboplastin very slowly into the plasma. Fonio (269) agrees with this, and he describes the characteristic changes during disintegration. Quick (279) described tests to detect platelet stability in this disease, and Heyl (280) reported certain presumptive tests to aid in detecting women who are carriers of the disease. If such tests could be developed to the point of complete reliability, obvious problems of eugenics might merit consideration. Macklin (281) presented additional data on the heredity of hemophilia. For recent literature of hemophilia, the reader is referred to Howell (275) and McGavack (282).

*Miscellaneous observations.*—Ebbecke *et al.* (283) found that clotting is markedly inhibited by pressures of 1000 to 2000 atmospheres. On release of pressure a nonretractile clot forms. At lower pressures inhibition occurs (284) if the calcium concentration is not optimal. Fresh normal clotted blood shows (285) inhibited retraction with a pressure of 800 atmospheres. If retraction has already commenced it is checked by pressure, but retraction continues when the pressure is released. Much uncertainty prevails regarding the cause of these pressure effects. Ebbecke (286) has also made extensive studies regarding the effect of mechanical agitation upon the clotting mechanism. There are a number of interesting observations, but the theoretical aspects await further clarification.



## ERYTHROCYTES

Robscheit-Robbins & Whipple (287) made additional studies on dogs kept anemic through repeated hemorrhage. Normal dog blood contains 20 gm. hemoglobin per 100 cc. With moderate bleeding and mild anemia (11 g. per 100 cc.) the rate of hemoglobin formation was only two thirds as great as with extensive bleeding and severe anemia (6 gm. per 100 cc.). At this latter level it was found (288) that the plasma protein level remained almost normal in some cases, but in others it became stabilized 15 to 35 per cent below normal. In all cases the amount of hemoglobin formed per week (i.e., the amount removed by venesection) was approximately twice as great as the amount of plasma protein formed. Changes in the type of protein present in the diet seemed to have no influence on this ratio.

*Iron.*—Austoni *et al.* (289) employed radioactive iron in a study of absorption, distribution, and excretion of iron in normal and in iron-deficient rats. Waldenström (290) studied the theory of iron therapy, and found that the liver plays an important role in regulation of the iron level in the serum. Fowler & Barer (291) found that many individuals have a low ("normal") hemoglobin level. When iron is administered, the hemoglobin level usually rises for two months, and then declines, often to the original level, despite continued administration of iron. They believe that the rise represents a "stimulating action" of iron. It was also reported (292) that 12 to 15 mg. of iron a day is required to prevent negative balance. The balance level was the same for those who had hypochromic anemia as for those who did not.

Test-tube experiments by Hahn *et al.* (293) showed that neither erythrocytes nor free hemoglobin of anemic animals are able to absorb significant amounts of radioactive iron from plasma or saline solutions. In contrast, these workers previously found that in the intact animal a part of the injected iron promptly appears within circulating red cells.

Chemical studies (294, 295) have established the fact that blood contains a small percentage of inactive hemoglobin (containing ferric iron). This hemoglobin unites with carbon monoxide only after reduction with sodium hyposulphite. Tompsett (296, 297) found that ferric iron is very firmly bound to organic components of the plasma. Similar combinations prevent absorption



of iron from the intestinal tract. In an acid medium the iron is reduced to the ferrous state; it is then dialyzable and is readily absorbed. These observations are offered as an explanation of the fact that iron is not readily absorbed in patients having achlorhydria.

*Copper.*—In rats made anemic through copper deficiency, the bone marrow show very little cytochrome oxidase activity (298). Administration of copper restores this activity promptly. It is thought that this activity is essential to hematopoiesis.

In patients with hypochromic anemia, the supply of copper is apparently not a limiting factor (299). Frost *et al.* (300) found that, on a milk diet supplemented with iron and copper, many dogs form hemoglobin normally; others require cobalt in addition.

A comprehensive review of the role of metallic elements in blood formation has been published (301).

*Porphyrins; bilirubin; vitamins.*—Langen & Grotepass (302) stress the role of porphyrins as intermediates in hemoglobin formation. The rise in the blood porphyrin level in lead poisoning is replaced by a fall as the bone marrow becomes weakened. They isolated this porphyrin from the blood by means of chromatographic absorption of the methyl ester. The erythrocytes contained only protoporphyrin IX. The bone marrow of the experimental animals contained large amounts of protoporphyrin and smaller amounts of corprotoporphyrin.

Vannotti & Siegrist (303) studied hemoglobin formation and destruction *in vitro* in bone marrow preparations. They found hemoglobin formation and a concomitant decrease in bilirubin and free iron. As the preparation grew old, bilirubin and iron were again set free. Cultures from animals poisoned with lead had slight ability to form hemoglobin, but they did form porphyrins in large amounts. Bomford (304) injected bilirubin and iron into dogs made chronically anemic by repeated hemorrhage. Each substance was found to stimulate hemoglobin formation, and the two together were especially effective.

Street *et al.* (305) reported that dogs suffering from vitamin-B<sub>6</sub> deficiency have anemia which can be cured by giving this vitamin. Wolf & Seidel (306) found that this vitamin prevents the production of experimental anemia in rabbits by injection of typhoid toxin. For further data regarding vitamin B see Singer (307) and Falzoy (308).



Hogan *et al.* (309) presented evidence to indicate that "pigeon anemia" is due to deficiency of a previously unrecognized vitamin. Hogan *et al.* (310) reported that lysine prevents the anemia in rats fed a diet containing deaminized casein as the sole source of protein. The amount of lysine needed is two to four times normal requirements.

*Pernicious anemia.*—Meyer *et al.* (311) reported an additional case of pernicious anemia following gastric resection. Schenken *et al.* (312) found the antipernicious anemia factor to be present in the liver of a patient having carcinoma involving the entire stomach with the exception of the pylorus. In another patient the carcinoma replaced the pylorus only, and in this case the liver was devoid of the antianemic factor.

The literature concerning failure thus far to produce true pernicious anemia in animals through resection of the stomach has been reviewed (313, 314). Recently, Crandall *et al.* (315) found that dogs with internal biliary fistulas eventually develop a macrocytic anemia. This anemia does respond to liver extract and is thought to be due to faulty absorption of the maturation factor when bile is excluded from the intestine. Geiger *et al.* (316) removed the stomach of swine, and although they did not report a picture of pernicious anemia, they did report the suggestive finding that within six months the antipernicious anemia principle disappeared from the liver. When the stomach was isolated from the rest of the alimentary tract, but otherwise left in place, the antipernicious anemia factor also disappeared from the liver. This indicates, as Castle believed, that this factor results from gastric digestion and not from action of a hypothetical hormone produced by the stomach. These workers also present evidence to substantiate the data on man which indicated that the mucosa of the duodenum, like that of the stomach, is a source of the "intrinsic" factor.

Isaacs (317) injected 10 mg. daily doses of glycocholic acid subcutaneously into twelve rats. Within two weeks three of the rats developed a macrocytic anemia which, he believes, is counteracted by liver extract. He suggests that bile salt, in excess, may interfere with the secretion of the intrinsic factor.

Heinle *et al.* (318) report that liver extract is of no benefit in the treatment of the anemia associated with experimental cirrhosis produced in rats by the administration of carbon tetrachloride.



This observation leads them to question the thesis that, clinically, the anemia of liver disease is related to true pernicious anemia.

Wilkinson *et al.* (319) reported an excretion of the antipernicious anemia factor in the urine. Formiyne (320) found that the extrinsic factor of Castle passes through an ultrafilter. On the basis of alcohol solubility, mainly, he believes that no reaction occurs between intrinsic and extrinsic factor *in vitro*. He believes that the reaction occurs only within the body, probably in the wall of the intestine.

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DEPARTMENT OF PATHOLOGY  
STATE UNIVERSITY OF IOWA  
IOWA CITY, IOWA



## THE DIGESTIVE SYSTEM<sup>1</sup>

BY EDWARD J. VAN LIERE<sup>2</sup>

*Department of Physiology,  
West Virginia University, Medical School,  
Morgantown, West Virginia*

*Salivary secretion.*—According to Steggerda (1), fluid intake is not greater in man in the absence of salivary glands, and water and salt metabolism are not disturbed. Sanders (2) has noted the effects of sympathectomy and complete denervation on the volume and composition of saliva secreted through a common fistula of the submaxillary and sublingual ducts. Brassfield & Hands (3) studied changes in pH and rate of flow of submaxillary saliva during acetylcholine stimulation after inducing changes in pH of arterial blood by varying oxygen or carbon dioxide tension or by injection of lactic acid or sodium bicarbonate. Increase in pH is associated with increase in volume of saliva, while decrease of pH inhibits secretion. The experimental changes induced are compared with those obtained by stimulation with pilocarpine and it is suggested that pilocarpine and variations in pH both have effects upon cell permeability.

*Gastric secretion and absorption.*—Gray, Bucher & Harman (4) concluded from their work that present theories explaining variations in composition of gastric juice are inadequate. An incomplete theory has been proposed (5) stating that the mechanism which concentrates and secretes chloride and bromide acts only through the negative charges on the ions. Genuine secretory activity has been shown to occur in isolated gastric mucosa of the frog (6). Radioactive chloride passes rapidly from the blood to gastric juice even in achlorhydria, in which the relatively slower appearance is due to smaller volume of secretion (7). Van Liere & Vaughan (8) have shown that severe anoxia depresses the volume of basal secretion in Pavlov dogs, although mild anoxia affects basal secretion less than that provoked by food. Acid and chloride content and pH of the basal secretion are not appreciably altered by anoxia. Secretion of acid after various extensive surgical procedures on the

<sup>1</sup> This review covers the period from July 1, 1940 to July 1, 1941.

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distal end of the stomach has been measured (9). Varco & Visscher (10), reinvestigating a list of acid dyes reported to be secreted in gastric juice, stated their work supported the earlier generalization that only dyes with chromogen cations are secreted in acid gastric secretion. Lifson *et al.* (11) concluded that osmotic activity and sodium content of pouch juice are related.

Comprehensive studies have been reported of the comparative efficacies of various antacids (12, 13) and of their effects on contents of the stomach, pylorus, and duodenum (14). Haggard & Greenberg (15) reported that certain fruit juices briefly influence the pH of gastric juice but do not seriously retard peptic activity or emptying of the stomach. Orange juice causes a higher free acidity (with a peak in one hour) than either the Ewald meal or top milk (16). Aluminum salts inactivate pepsin at pH 1 to 2; and pepsin is precipitated by aluminum hydroxide or phosphate at a slightly higher pH (17).

Bucher & Ivy (18) concluded that the double histamine test has certain limitations in quantitative study of pepsin secretion. Histamine has as direct a stimulant action on cells secreting pepsin as does pilocarpine, although treatment with pilocarpine yields more pepsin (19). Histamine released through immersion of the hand in water at 10°C. or the entire body at 75°C. produced an effect on gastric acidity fifteen minutes following these procedures. This effect is antagonized by intraduodenal administration of histaminase (20), although histaminase has no effect on the secretory response to histamine in man or dogs with complete or Heidenhain pouches (21). Intramuscular injection of yeast extract has an histamine-like effect on gastric secretion in the dog but it is believed that the active principle is not histamine (22). Gray, Wieczorowski & Ivy (23) reported that subcutaneous injection of urogastrone in man significantly diminishes the gastric secretory response to histamine. Babkin (24) has shown that parathyroid hormone (parathormone) also decreases the secretory response to histamine and test meals. This inhibition persists for several weeks after administration has been discontinued and the calcium concentration of the serum has returned to normal levels. Although prolonged administration of activated ergosterol produces a similar effect on serum calcium, this agent does not seem to alter the secretory response to histamine. Elliott (25), who used a different parathyroid preparation, reported an increase of free and total acidity



and peptic activity during hypercalcemia; intravenous injection of calcium lactate or chloride inhibited secretory responses to vagal stimulation and histamine (26). The concentration of calcium in the juice is directly related to the buffering capacity in these experiments (27).

Ehrenfeld & Sturtevant (28) found a significant increase in gastric acidity after the smoking of two cigarettes; the increase was less with denicotinized cigarettes. It was not stated whether the experiments were performed on habitual smokers. If olive oil or cod liver oil is fed a dog with a Pavlov pouch before a test meal, the volume, acidity, and pepsin content of the pouch secretion is reduced (29). Sublethal subcutaneous doses of thymoxyethyldiethylamine do not influence the secretory response to histamine (30). Negligible inhibition of acid gastric secretion is produced in dogs with plasma contents of less than 10 mg. per cent of sulfanilamide, while 20 to 40 per cent inhibition of acid secretion occurs at 25 mg. per cent (31). Section of the stalk of the pituitary does not alter the pH or total or free acidity of gastric juice, but the volume is decreased about 25 per cent (32). Wells & Gray (33) reported that hypersecretion, following enterectomy, may be due to stimulant effects of the procedure and postoperative care rather than to surgical elimination of enterogastrone.

Gray *et al.* (34) concluded that the active principles of urogastrome and pituitrin are separate entities. If there is but a single substance in urine which affects gastric secretion, it does not arise from the intestine (35).

Necheles *et al.* (36) stated that histaminase has no effect on salivary, gastric, biliary, or pancreatic secretion of dogs treated with histamine and also that it has no effect on gastric secretion following a meat diet or on gastric motility after treatment with insulin or prostigmine.

Traumatic shock was found to have no effect on gastric secretion in studies of Necheles & Olson (37) while shock from burns causes a large increase in volume of gastric juice and in motility of the stomach. Other secretions of the alimentary tract are unaffected. These findings throw new light on the etiology of Curling's ulcer. Brunschwig *et al.* (38) reported the presence, in achlorhydric gastric juice of patients with gastric carcinoma, of a secretory depressant for Pavlov pouches in dogs.

In a study of free acidity in sixty-one normal subjects, Town-



send (39) concluded that estimation of total acidity is unnecessary when free hydrochloric acid is normal or high. Precision of the dilution indicator technique has been studied (40, 41) with the recommendation that it be used only with isotonic test meals. Palmer *et al.* (42) reported that transient, unexplained refractoriness to histamine is recognized and that histamine-proved achlorhydria does not necessarily indicate permanent anacidity. In a study of 121 patients with histamine-proved anacidity, Schindler *et al.* (43) found gross anatomical lesions in all but five cases.

Warren *et al.* (44) concluded from intubation studies in man that hypertonic solutions of glucose are absorbed from the stomach for a short time but that secretion of mucous prevents absorption thereafter. Histamine was found by Myant (45) to promote absorption by the gastric mucosa, of certain poorly absorbed substances, such as sulfate.

*Gastric motility.*—Quigley and his co-workers (46) have continued their study of the mechanism of gastric evacuation, with optical registration and fluoroscopic observations of antral and bulbar pressures. Gastric evacuation results from a pressure gradient from antrum to bulb, combined with propulsive antral peristalsis. These workers (47) believe that optical registration is superior to the ordinary water manometer method of recording gastrointestinal pressures. By the former technique, they found that basal pressure in the duodenal bulb is lower than that of the pyloric antrum and that both rise when food enters the stomach. Subatmospheric pressures are common in both regions, and the pressure changes usually are closely related in bulb and antrum. Even in vagotomized animals, swallowing or smelling of food briefly decreases these pressures, but this transient inhibition is quickly supplanted by phasic changes of greater magnitude after feeding. Introduction of cream into the duodenum of fasting dogs reduces or even reverses the antral-bulbar pressure gradient (48). Delay in gastric emptying is primarily dependent upon suppression of antral propulsive peristalsis.

Card (49) found that fatty acids are more effective than the corresponding neutral fats in inhibiting gastric motility, there being a linear relationship between amount of fatty acid and duration of inhibition. Shay *et al.* (50) reported that the gastric emptying time of man is decreased by hypertonic glucose solutions and that this effect is due to irritation of the duodenum.



Effect of various pharmacologic agents on gastric motility have been studied by several authors. The Grubers (51) found that tonus and amplitude of contraction decrease after most barbiturates but may increase with thiobarbiturates. Morrison & Feldman (52) reported that large doses of atropine suppress gastric motility of the dog to a greater degree than bilateral vagotomy, thus confirming the known effects of this agent in man (53). Thyroid substance does not inhibit the suppression of motility produced by atropine and the accelerating effect of thyroid therapy on motility is annulled if sufficient atropine is given to paralyze myoneural junctions. In man, gastric motility in the hypothyroid state has been studied by Hamilton *et al.* (54), who found that, as the metabolic rate is increased by therapy, the gastric motility becomes normal and abdominal discomfort disappears. Extracts of anterior pituitary have no effect on gastric emptying time in dogs (55), and hypophysectomy does not influence gastrointestinal motility. Normal female human urine extract inhibits gastric motility (56) but it is not definitely shown that the same component is responsible for inhibition of both gastric secretion and motility (57). Introduction of solutions of bile salts into the stomach of fasting dogs during the contraction phase produces inhibition (58) but hunger contractions result during the quiescent phase. Fetter (59) has shown that 0.1 N HCl evokes gastric contractions in the stomach of turtles, and that one to two cat units of strophanthin inhibit gastric motility and cause pyloric constriction. Confirming observations in man (61), Smith & Penrod found that amphetamine causes relaxation of the stomach of rats (60), constricts the pylorus, and delays propulsion of material along the gastrointestinal tract.

Controlled studies have been made of effects of therapeutic doses of commonly used agents on gastric emptying time in young men. Van Liere & Northup (62) found that oral doses of 425 mg. ( $6\frac{1}{2}$  gr.) of dehydrocholic acid produce a mean decrease of 21.2 per cent and that doses of 1.0 gm. of sulfapyridine (63) produce a mean increase of 28.6 per cent, with considerable individual variation. The mean blood level of sulfapyridine near the completion of gastric emptying in the latter experiments was 1.8 mg. per cent. Sleeth & Van Liere (64) reported that doses of 65 mg. of sodium nitrite cause a mean delay of 23.6 per cent in the gastric emptying time of seven subjects. Marked individual variations were noted, from



practically no effect in one instance to a delay of 65 per cent in another.

Hesser *et al.* (65) found that ablation of the motor cortices of cats resulted in a demonstrable increase of stomach contractions and increased tone, which was interpreted as evidence of release from a regulating influence of the motor cortex. They suggested, "that the smooth muscle of the stomach and esophagus is controlled by reflex pathways in the nervous system similar to those which control tone and contraction in the vesical muscle."

The effects of psychic phenomena on the movements of the empty stomach have been reported (66).

Bisgard & Nye (67) found that heat applied to the abdominal wall inhibits motor activity of the stomach and intestinal tract while, conversely, cold stimulates contractions. If hot or cold fluids are taken orally, these thermal responses are reversed.

The Grubers (51) were unable to confirm the suggestion (68) that amytal causes contraction of the pyloric sphincter of dogs. In the rat, amphetamine produces constriction of the pylorus (60). The observations have been made (69) gastroscopically that the opening of a gastroenterostomy has a sphincter-like action very similar to that of the pylorus.

*Intestinal motility.*—Becker & Windle (70) observed that localized contraction of the intestine in response to stimuli occurs in cat and guinea pig fetuses on the twenty-fifth to twenty-seventh day of gestation and that spontaneous gastric and intestinal peristalses appear in the cat at twenty-nine to thirty days and in the guinea pig at thirty-five days, reaching a maximum at fifty days, followed by a decline. Mecray (71) made fluoroscopic observations of the duodenum of cats and dogs after sterile injection of thorotrast into the serosa, and noted the occurrence of pendular movements, changes in length and periods of increased tonus; classic peristalses were not seen. Two previously undescribed types of intestinal activity were recognized, namely, a twisting movement through 45°, and an apparent gradual opening of the lumen before passage of a trickle of barium sulfate suspension. Forster (72) studied motility of the lower small intestine in a male patient with a prolapse through which a loop of ileum was exteriorized. Peristaltic waves, effective in propulsion in the lower three feet of the small intestine, occur 106 times in thirty minutes, lasting from one to six minutes. Activity, interpreted as mixing waves, occurs 9 to 150



times in thirty minutes and is ineffective in propulsion. Morphine suppresses peristalsis and increases the frequency of mixing waves while atropine inhibits both.

Stimulation of the hypothalamus anterior to the infundibulum was observed by Wang *et al.* (73) to produce immediate blanching and occasional inhibition of motility of the intestine of fasting cats, followed by an excitatory phase lasting for several minutes and unaffected by section of both vagi. Vagal effects are noted after stimulation of the region behind the infundibulum. Similar responses occur in chronic spinal cats but are abolished by bilateral vagotomy. Douglas & Mann (74) reported effects of peritoneal irritation on activity of the intestine, and noted arrest of movements following degeneration after section of both vagi, after section of one splanchnic nerve, and after adrenalectomy, but no permanent arrest was found after section of both splanchnics. Since observations were made on exteriorized loops, the authors suggest that the effects are a reflex inhibition inasmuch as the stimuli are delivered to afferents other than those in the loop; they consider that there is a sound physiologic basis for the neurogenic concept of paralytic ileus. Oppenheimer & Mann (75) noted in exteriorized loops in dogs that intestinal activity precedes vomiting and presumably is antiperistaltic. They (76) also used the same technique in determining that various cathartics influence amplitude and character of contractions but not the frequency. Of the agents used, cascara sagrada least disturbed motility and feeding responses. Youmans *et al.* (77) recorded motility of the human small intestine by motion pictures of an abdominal hernia. Prostigmine caused a marked stimulation not entirely antagonized by atropine, and pituitrin inhibited motility of the visible portion of the intestine.

Glyer & Oppenheimer (78) observed that neither thyroid extract nor dinitrophenol has any appreciable effect on the rate of contraction of loops of small intestine. Dick & Hege (79) found that thiamin has no effect on isolated rat intestine even though perfused through the lumen, but that the intestine of thiamin-deficient rats shows increased peristalsis and retardation of the rate of loss of tonus within ten minutes after addition of thiamin. Large doses of novatropine inhibit tone and motility in anesthetized and unanesthetized human beings (80).

Starkenstein (81) made the interesting observation that anoxia



antagonizes the inhibitory action of epinephrine on isolated intestine and that restoration of the oxygen supply will permit the normal inhibitory response for as long as twenty minutes after epinephrine is added to the anoxic strip. If epinephrine or its oxidation products are administered repeatedly, the effect of anoxia becomes less pronounced. He relates this phenomenon to carbohydrate metabolism of the intestine.

*Intestinal absorption and secretion.*—In further study of the mechanism of absorption, Wells (82) found that the rate of absorption of isotonic saline is retarded by moderate congestion of mesenteric veins and lymphatics. "Absorbing and secreting forces should be neutralized when the difference between mean capillary pressure in the villi and intra-intestinal pressure is equal to the colloid osmotic pressure of the animal's blood plasma." Rate of secretion of intestinal juice increases geometrically with increase in mesenteric venous pressure above the level required to abolish absorption. Dennis & Visscher (83) studied the rate of absorption of water and salts from chronic ileal loops in unanesthetized dogs and found that a roughly linear decrease of volume occurs during the initial ten minutes of absorption. In originally isotonic mixtures of sodium sulfate and chloride, the chloride clearance is a direct but nonlinear function of sulfate concentration and the absolute absorption rates of the sodium salts are direct functions of their individual concentrations. Net fluid absorption is inversely related to concentration of sulfate in the mixture but not linearly so, and the net solute is not equal to the calculated osmotic equivalent of water of the salt moved. "The probable mechanism is a two way movement, that is, the hypotonic solution enters and the hypertonic salt solution leaves."

Driver (84) concludes from studies of the effects of hexylresorcinol on the absorption of chloride, glucose, and sulfite, that a special biologic agent is responsible for absorption of electrolytes as well as other substances. Calcium is best absorbed from highly acid solution (85). Adrenalectomy was shown by Stein & Wertheimer (86) to retard absorption of chloride in the rat and to prevent absorption against a concentration gradient. Desoxycorticosterone restores normal absorption. Rats maintained on a thiamin-free diet do not suffer from interference with normal active absorption of ions. Thyrotoxic animals show no clear deviations from controls. Monoiodoacetate completely inhibits absorp-



tion of ions against a concentration gradient. Sodium taurocholate or glycocholate (87) in concentrations of 1.5 per cent decreases chloride absorption. In the lower ileum, where absorption against a concentration gradient is most rapid, the concentration of bile salts does not reach 1.5 per cent. The absorption of iron from an average diet is not greatly reduced in the absence of bile (88).

In man, intestinal intubation studies made by McGee & Emery (89) show that most of the nitrogen of a 4 to 5 per cent solution of casein and gelatin is absorbed forty to fifty minutes after introduction into the jejunum. Nitrogen of an amino acid mixture from hydrolyzed casein is similarly absorbed in fifteen to twenty-five minutes. The Miller-Abbott technique of intubation has also been applied to man in a study of absorption of an enzymatic hydrolysate of casein (90). In open loops of the upper jejunum, the nitrogen content of such solutions is always diluted to 2 mg. per cc. in thirty minutes, regardless of the initial concentration. This constancy does not apply to closed loops. Absorption of nitrogen in this mixture varies with the original amount introduced; from a 5 per cent hydrolysate 98 per cent is absorbed and from a 10 per cent hydrolysate 72 per cent is absorbed in open loops. Rate of absorption of a 15 per cent mixture from closed loops is only slightly more than with a 10 per cent mixture.

Houssay and co-workers (91) found that intestinal absorption of glucose, galactose, and xylose by the toad is not modified by insufficiency of the pituitary or adrenal glands even though the resultant asthenia and intestinal dilatation may be marked. Surgical manipulation and post-operative anorexia are responsible for decreased absorption of glucose in adrenalectomized animals (92), since sham operations also decrease absorption. Fasting causes a slight decrease in absorption of glucose. In man, Shay *et al.* (50) showed Cori's finding that the rate of absorption was independent of the absolute amount and initial concentration of glucose may be attributed to retardation of gastric emptying and to the dilution mechanism of the duodenum. The duodenum absorbs glucose more rapidly than other portions of the intestinal tract of man but the rate is variable from day to day (93). It also was shown in man that much more glucose is absorbed from the gastroduodenal than from the jejunoileal region (94).

Pachman (95) found that the decrease in oral glucose tolerance which occurs in thiamin-deficient rats is not due to factors in ab-



sorption, since tolerance also is decreased toward intravenous injection of glucose.

Of a number of optically active pentoses, *d*(+)-xylose is the most rapidly absorbed by the rat (96). It is suggestive that this pentose has the same configuration at carbon atoms 2, 3, and 4 as dextrose.

Deuel and co-workers have made further studies of intestinal absorption of natural and synthetic fats. No consistent differences are noted in rates of absorption of hydrogenated or wintered cottonseed oil, butter fat, or coconut oil (97). Triacetin and tributyrin are absorbed more rapidly by the rat than other natural or synthetic fats studied (98). Neutral fats containing odd-chain fatty acids are absorbed less than half as rapidly as the corresponding fats containing even-chain fatty acids (99). Since butyric, caproic, and caprylic acids are absorbed more rapidly than propionic, valeric, and heptonic acids, the differences in rates of absorption of triglycerides composed of even- and odd-chain fatty acids are due to differences in rate of removal of the component fatty acids. There is no significant difference in rates of absorption of chaulmoogra and olive oils, or sodium chaulmoograte and oleate in the rat (100).

Bile and pancreatic lipase both favor absorption of carotene (101). When these substances are used together, maximal absorption is obtained and nearly complete failure of absorption occurs in the absence of both agents. Vitamin-A esters behave as do esters of fatty acids in the intestine (102). They are hydrolyzed enzymatically and the vitamin occurs in intestinal mucosa chiefly as the alcohol during the height of absorption in the rat.

Stockholm and her co-workers (103) believe that phosphorylation is not essential for intestinal absorption of thiamin, which is probably dependent upon simple diffusion.

Driver & Murlin (104) found that several substances promote the absorption of insulin from intestinal loops but noted a shorter influence on blood sugar than if insulin were given subcutaneously. There is no direct relation between surface tension effects of agents used and their promotion of absorption of insulin. Hanzlik & Cutting (105), on the other hand, found that the most consistent absorption of insulin occurs in the presence of agents which lower surface tension and they believe that inhibition of enzymatic activity, combined with local surface effects on cells, is an important factor in furthering enteral absorption of insulin. Quinine sulfate



best satisfied both requirements among agents tested. Seven of ten diabetic patients reacted well to oral administration of an insulin-quinine mixture but routine clinical use is not recommended (106).

Citric acid in doses of 1 gm. per kg. is rapidly absorbed by the rat and the rate of absorption is related to the amount present in the intestinal tract (107). Among the sulfonamides, sulfanilylguanidine is poorly absorbed and is used successfully as a chemotherapeutic agent in bacillary dysentery (108). Numerous studies of absorption of other sulfonamides have appeared, based on the presence of these substances in the blood; direct studies are lacking. Absorption of guaiacol and thymol derivatives has been demonstrated after oral administration to rabbits (109). Travell & Gold (110) found that only about 25 per cent of tincture of digitalis is absorbed from the gastrointestinal tract of cats, whereas practically all of digitoxin-like preparations are absorbed; similar findings were reported in man.

Fink & Nasset (111) have reported that ingestion of thiocyanate doubles or sometimes quadruples the volume and total enzyme and mucoprotein of the ileal and colonic secretion but that the chloride and carbon dioxide content is not affected and there is no effect on metabolism of the intestinal mucosa. Duckworth & Godden (112) found that an increase in fiber intake in the rat augmented the fecal phosphatase excretion, which they felt indicated increased secretory activity within the intestine.

*Pancreas.*—Greengard, Stein & Ivy (113) found that the increment in secretion, on increasing the dosage of secretin, is rapid with small doses and gradual with larger doses, with attainment ultimately of a maximum flow. Analogous results were obtained through continuous administration of secretin. These workers (114) feel that secretin is inactivated enzymatically and that dog, beef, and human blood contain a secretinase. Osborn & Greengard (115) observed a seven-fold increase in the rate of secretion in secretin-treated dogs when the body temperature was subsequently raised, and complete cessation of secretion when the body temperature was lowered. Thomas & Crider (116) reported that the threshold acidity of intestinal contents effective in promoting pancreatic secretion is about pH 4 in dogs during digestion of meat and that this pH commonly occurs in the duodenum under these circumstances, thereby effecting a natural adequate stimulus. They (117) concluded also that the increased flow of pancreatic



juice, induced by the presence of bile in the intestinal contents, occurs only under special conditions, all of which are probably abnormal.

Scott *et al.* (118) studied the periodic activity of the stomach and pancreas and failed to confirm the regularity and correlation claimed by Boldyreff. The outflow of pancreatic juice in fasting dogs with fistulae shows marked irregularities (119) and a critical study is presented of different types of fistulae. In man, Diamond *et al.* (120) concluded from results of 130 tests performed on 104 patients that the secretin test supplies information concerning the function of the pancreas and is of diagnostic value in pancreatic disease. Comfort & Osterberg (121) compared effects of secretin and acetyl- $\beta$ -methylcholine on pancreatic secretion in man and found that secretin markedly increases volume and pH, and reduces the concentration of enzymes while the choline derivative increases the volume but slightly, does not affect pH, and causes a prolonged increase in the concentration of enzymes.

Urine apparently contains both a thermolabile factor acting on secretin and a thermostable factor directly affecting secretory activity of the pancreas (122).

The insulin content of the pancreas does not differ from normal either in adrenalectomized rats or rats fed daily with a potent adrenal extract (123). Kauer & Glenn (124) found it necessary to remove 84 per cent of the pancreas of dogs before diabetes develops. Whipple & Bauman (125) observed no disturbance in glucose tolerance tests nor in digestion and absorption of food in three patients from whom 75 per cent of the pancreas had been removed. They felt that normal fat absorption is possible when no pancreatic juice enters the intestine, although Beazell *et al.* (126) state that the literature shows that a decided impairment in digestion and absorption of fat occurs in the absence of pancreatic juice in experimental animals. In four cases of achylia pancreatica (126), enzyme therapy decreased fat and nitrogen excretion in the stools, and a clinical response, characterized by decrease in frequency and bulk of stools and gains in weight and strength, was manifested in a few days.

Ball *et al.* (127) postulated that the bicarbonate of pancreatic juice arises from the serum and not from metabolic carbon dioxide of the pancreas. Taylor & Ågren (128) showed that sulfapyridine is secreted in the pancreatic juice of cats in a concentration slightly



below that of the blood. Montgomery and co-workers (129) found that radioactive sodium appears in pancreatic juice within three minutes after intravenous injection and that a maximum concentration occurs within fifteen minutes.

Elman & Sachar (130) have reviewed the literature concerning the pancreas for the year 1940.

*Colon*.—Becker *et al.* (131) have stated that, while deglutition may occur as early as the forty-second day in the fetal guinea pig, defecation does not occur *in amnio* until late in the gestation period (not before the sixtieth day). Relations between transportation force and motility of the colon of dogs were studied by Templeton & Adler (132), who conclude that transportation force is intimately related to the active period and that apparent intensity of an active period is not necessarily indicative of the amount of transportation force. Adler *et al.* (133) have shown in colostomized men that the same types of motility occur in the proximal portion of the descending colon as in dogs, and recognize contractions of types I, II, and III. The quantity and quality of motility vary between individuals and also in the same individual.

Several studies of effects of various agents on motility have been reported. Haag & Taliaferro (134) found that in concentrations up to 10 mg. per cent ascorbic acid greatly increases tone of isolated guinea pig colon, and they correlate this with known clinical side effects of this substance. Minimum effective concentrations of amphetamine stimulate the isolated colon (60) but higher concentrations inhibit motility. Adler *et al.* (135) showed that intravenous injection of dilute alcohol slightly inhibits nonpropulsive motility of the colon of appendicostomized dogs but that propulsive motility is increased by either intravenous or intragastric administration of alcohol. In colostomized men, administration of 250 cc. of 20 per cent whiskey does not affect frequency of nonpropulsive motility of the distal colon but tends to stimulate propulsive motility and usually facilitates the gastrocolic reflex evoked by a meal. Adler *et al.* (136) also found that intravenous injection of *E. coli*, *Staph. aureus*, or *Spirillum rubrum* in cecotomized dogs is followed by depression of colonic motility of slow onset and long duration, as well as by certain systemic symptoms including nausea, vomiting, and defecation.

Adler & Ivy (137) reported that appropriate subcutaneous doses of morphine sulfate cause an increase in tone and both pro-



pulsive and nonpropulsive motility of the colon of dogs. Premedication with atropine antagonizes the effect of morphine on propulsive motility but does not alter appreciably the effects on tone and nonpropulsive motility. Spontaneous motility is depressed for an hour or more after injection of 1 mg. of atropine, and recovery is more rapid in the proximal than in the distal colon. In cecotomized dogs, Templeton & Adler (138) found that morphine causes an immediate augmentation followed by a retardation of rate of movement of a bolus, which is interpreted by them to indicate a primary augmentation and secondary retardation of the "efficiency gradient"; this retardation is held responsible for the constipation following morphine administration. Immediate effects of small subcutaneous doses of morphine include a marked increase in tone of the colon and often a disappearance of quiescent periods (139). No tolerance appears to repeated daily doses of one-fourth grain of morphine, nor are cumulative effects noted over a period of sixty days; colon motility returns to normal within twenty-four hours after subcutaneous injection of one-fourth grain of morphine.

Adler & Atkinson (140) studied the synergistic effects of pituitrin, physostigmine, prostigmine, and ergotamine on colonic motility in colostomized men. All but ergotamine increase propulsive motility when administered alone, and various combinations are strongly active in stimulating propulsive motility.

Turell *et al.* (141) found that sulfanilamide is absorbed from the rectum and colon best when given in solution but also when given as suppositories.

*Gastrointestinal ulcer.*—It has been reported by Mulsow (142) that about one third of deaths from peptic ulcer occur in patients over sixty years of age and nearly one third during the sixth decade of life. The situation of ulcers recurring after operation is in or near the site of surgical anastomosis at the point of maximal impingement of chyme, and these secondary ulcers often penetrate deeply (143). Volume of nocturnal gastric secretion is larger in patients with ulcers than in controls but the concentration of free acid is similar (144). Patients with recurrent ulcers do not regularly exhibit gastric anacidity following high gastric resection (145) and, while achlorhydria usually results from resection with gastrojejunostomy and may accompany extensive resection when pylorus and antrum remain, extensive resection *per se* does not necessarily



cause achlorhydria (146). Perfusion with pepsin and hydrochloric acid is capable of causing perforation of the duodenum within twelve hours; perfusion with hydrochloric acid of pH 1 alone causes necrosis and damage to villi (147). Efficacy of various antacids has been tested in patients with peptic ulcer and in Mann-Williamson dogs. The more effective agents are: milk, tribasic calcium or magnesium phosphates (148); gelatin (149); aluminum phosphate gel (150); and magnesium trisilicate (151). Aluminum hydroxide is contraindicated under certain conditions (152). Shay *et al.* (153) have reviewed the physiologic significance of gastric anacidity.

Conditions found to favor gastrointestinal ulceration include: malnutrition (154); vitamin-C deficiency (155); severe starvation before certain diets (156); and treatment with acetylcholine in physostigminized animals or with choline alone (157). According to Boles & Riggs (158), neurogenic ulcer is a focal manifestation of subclinical general circulatory insufficiency caused by effects of primary intracerebral disease on the central vegetative mechanisms or, if cerebral disease does not exist, of autonomic disturbances resulting from circulatory insufficiency.

It was reported that enterogastrone prevents development of gastroduodenal ulcers (159) and the anterior-pituitary-like hormone deters progress of ulcers in Mann-Williamson dogs (160).

*Miscellaneous.*—Bayliss (161) found that staphylococcus enterotoxin causes vomiting in cats when given intravenously, intraperitoneally, and intracardially but not when given orally, intramuscularly, or subcutaneously; he concluded that the emetic effect is due chiefly to stimulation of sensory endings of the small intestine with the efferent path along the vagi. Emetic effects of sulfapyridine were studied by Sadusk *et al.* (162) who concluded that this response is not due to irritation of the stomach or direct action on the vomiting center but to reflex stimulation from sites other than the gastrointestinal tract.

Dragstedt and co-workers have continued their study of lipocaic. There is no relation between lipocaic and ketogenesis (163). Hypophysectomy does not prevent fatty infiltration of the liver in depancreatized animals (164). In rabbits fed cholesterol, deposition of this substance is not prevented by purified lipocaic (165); this finding confirms studies of the effects of crude preparations. Clark *et al.* (166) have substantiated the clinical inference that xanthomata are associated with disturbance of fat metabolism,



and believe that lipocaic may prove to be a valuable adjunct in therapy.

Montgomery *et al.* (167) challenged the assertion (168) that fatty changes in the liver in depancreatized dogs maintained on insulin are not due to absence of pancreatic juice from the intestine, and stated that this action establishes an essential function for pancreatic juice, daily liberation of which is necessary for prevention of excessive deposition of fat in the liver, although the mechanism is obscure. Their findings are similar to those in a previous study of effects of raw pancreas in dogs with ligation of pancreatic ducts (169). Parallel studies show the effect of daily administration of fresh pancreatic juice (170) or raw pancreas (171) on blood levels of cholesterol, phospholipids, and fatty acids.

Lawson & Chumley (172) suggested that local reflex vasodilation occurs on distention of loops of ileum in barbitalized dogs. Kuntz & Haselwood (173) explain the circulatory changes in the viscera produced by localized cutaneous stimulation as the result of the action of segmental and intersegmental cutaneovisceral reflex arcs. Todd *et al.* (174) reported further observations of digestion and absorption in a man with but three feet of small intestine remaining. They found that carbohydrates are utilized normally in this instance but that proteins are not as completely absorbed and that excretion of fat in the feces results in major losses of calcium and phosphorus, necessitating a high calcium diet fortified with viosterol to avert tetany. Chunn & Harkins (175) observed that alimentary azotemia resulting from intestinal absorption of blood is due primarily to nitrogen from the hemoglobin and that the protein fraction is most important. Alimentary azotemia of this type results only from the presence of blood in the upper portion of the intestinal tract (176). Flaxman (177) has noted gastrointestinal manifestations of cardiac disease and discussed the most common complaints. Gastrointestinal symptoms which occur in some 10 per cent of cardiac patients persist until the cardiac condition is relieved. Concomitant cardiac and gastrointestinal disease is relatively uncommon. Acute edema of the pancreas, gallbladder, and stomach in serum anaphylaxis was reported by Auer & Krueger (178), who suggest that this effect may originate or exacerbate abnormal conditions in these organs. Histamine has similar effects (179). Klemperer *et al.* (180) have presented evidence supporting the vasospastic theory of intestinal lesions in shock.



The reciprocal innervation of the intestine has been studied by Hodes (181). Youmans (182) concluded that motility of innervated intestine at the site of distention depends, in part, on a balance between direct stimulant and reflex inhibitory effects. Patterson & Dunn (183) found that distention of the urinary bladder with pressures above 38 mm. Hg may reflexly inhibit the tonus and amplitude of gastric contractions, and stated that the chief pathways of this reflex are presacral.

Dickens & Weil-Malherbe (184) measured the metabolism in tissue slices from various parts of the intestine. The jejunal mucous membrane has a higher metabolic rate than that of the ileum or the colon.

Antonicic & Lawson (185) found that denervation does not significantly alter motility of closed-loop obstructions in dogs and did not find evidence for existence of a special toxin in intestinal obstruction. Fine & Gendel (186) found intravenous injection of plasma to be more efficacious than saline in antagonizing the lethal effects of plasma loss from obstruction and distention of the small intestine of dogs. They feel that plasma loss persists for the duration of obstruction and, if it is uncompensated, death may be due solely to it. In a clinical study it was found (187) that patients with distention of the small intestine show a marked loss of plasma not due to dehydration or loss of electrolyte. Plasma volume is restored on decompression of the intestine. Glenn (188) reported that intubation is beneficial in the therapy of paralytic ileus by prevention of kinking postoperatively and in relieving symptoms of preoperative mechanical obstruction, but is not suitable for patients with intestinal strangulation.

The amount of colonic flatus normally excreted has been studied by Beazell & Ivy (189). In five ambulatory subjects, the mean volume was 527 cc. a day with extremes of 380 and 655 cc. No regular difference was noted between excretion during the day and night. The total amount of gas ejected per day is probably larger, since gas passed during defecation was not measured. According to Oppenheimer (190), healthy individuals expel gas whenever the amount in the intestine exceeds a threshold and excites peristalsis. In subjects with irritable intestine, from any cause, smaller amounts stimulate peristalsis and a sensation of distention is perceived even though little gas is present. Excessively large amounts of gas may fill the intestines when these are atonic.



Several new techniques deserve mention. Methods or modifications have been developed for the following: estimation of hydrogen sulfide in gastric contents (191); gravimetric oncometry of the intestine of the dog (192); and preparation of isolated intestinal loops in the dog (193). Thomas (194) has described a new type of cannula for gastric and intestinal fistulae. The reticulocyte response in rats has been criticized by Schlicke as unreliable in testing anti-anemic agents, particularly human gastric juice (195). Bloomfield *et al.* (196) have used the basal gastric secretion as a clinical test for gastric function, especially in cases of peptic ulcer. Various other methods or improvements are noted in the body of this review (18, 39, 40).

Reviews have been made during the year by Beazell & Ivy (197), on effects of alcohol on the digestive tract; by Van Liere (198), on effects of anoxia on the alimentary tract; by Florey, Wright & Jennings (199), on the secretion of the intestine; by Frazer (200), on fat absorption and its relation to fat metabolism.

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DEPARTMENT OF PHYSIOLOGY  
WEST VIRGINIA UNIVERSITY, MEDICAL SCHOOL  
MORGANTOWN, WEST VIRGINIA



# KIDNEY<sup>1</sup>

BY JAMES A. SHANNON

*Department of Medicine, New York University College of Medicine  
and the Research Service, Third (N. Y. U.) Medical Division,  
Welfare Hospital, New York, New York*

## DISCRETE RENAL PROCESSES

The discrete processes which contribute to the over-all functions of the kidney have received considerable attention during the past year. These have been studied from the viewpoints of evaluation, control, and integration one with another, and with extrarenal variables insofar as they participate in the control of more general physiological functions.

*Glomerular filtration.*—The belief that the polysaccharide inulin may be safely used as a precise measure of glomerular filtration rate in the vertebrates has been strengthened. The simultaneously observed plasma clearances of inulin and exogenous creatinine are identical in the reptile (1), a situation also true for the frog and for all mammals examined to date with the exception of man (2) and some of the infrahuman primates. A similar identity exists in the normal dog and man between the plasma clearances of inulin, certain hexitols (sorbitol, mannitol, dulcitol), and a hexitol derivative (sorbitan) (3). This demonstration in man is particularly important as is the extension of the linear relationship between plasma concentration and the renal excretion of inulin to the lower levels (4).

The difficulties which limit the usefulness of inulin in the renal problems of clinical medicine are practical rather than theoretical in origin. These arise from the precautions necessary in its preparation and administration as well as in its chemical determination and have led to the continued search for a simplification of the conditions surrounding its use and for a substitute substance. For certain purposes the single injection technique, either intravenous (5) or subcutaneous (6) has been shown to be quite adequate. Furthermore, the introduction of a term to correct for the volume of dis-

<sup>1</sup> This review covers the period July 1, 1940, to June 30, 1941. Articles published outside this period have been included only if the data contained therein greatly clarified one or another of the aspects of renal physiology under consideration. In several instances the references to completed reports have been substituted for those of the preliminary articles which were available during the preparation of the manuscript.



tribution of inulin would place the indirect determination of inulin clearance by its rate of disappearance from the plasma (7) upon a less empirical basis. This technique should be quite useful not only in the infant, for which it was devised, but also for small animals in general where urine collections are similarly difficult. It is emphasized, however, that these simplifying procedures will yield valid information only as their limitations are fully appreciated.

Endogenous creatinine has again been advanced as a substitute for inulin in the evaluation of glomerular filtration rate in man (8). This suggestion rests upon experiments which compare the simultaneously determined inulin and endogenous creatinine clearances, and upon considerations of the nature and chemical determination of the latter substance. The comparison of the two clearances has not the precision necessary to establish the authors' claim for endogenous creatinine, nor is the chemical determination of this substance in plasma by the Jaffé reaction sufficiently specific (3). It may be definitely stated that the available evidence on the renal excretion of endogenous creatinine in normal man is opposed to its acceptance for any renal measurement other than the gross approximation of glomerular filtration rate. Most certainly the precision of this approximation is not sufficient for use in combined observations which are aimed at the quantitative evaluation of tubular function (cf. 9). Further work supports the earlier assertion that exogenous creatinine is excreted in part by a tubular mechanism in the human kidney (2). The vagaries of this system as compared to other transfer mechanisms appear to be due to a change in the chemical nature of some of the administered creatinine. The effect of this change is exaggerated when observations are for long periods of time after a single oral dose and minimized when the material is given by constant intravenous infusion.

The excretion of hemoglobin has been studied in the normal dog in an attempt to characterize the pore size of the glomerular membrane. The relationship between plasma hemoglobin and its renal excretion was observed simultaneously with measurements of glomerular filtration rate by the creatinine clearance. These studies suggested to the authors (10) that hemoglobin is excreted by a combination of glomerular filtration and tubular reabsorption, that the permeability of the glomerular membrane is such that it would appear as if 3 per cent of its pores were sufficiently large to permit the free filtration of the hemoglobin molecule of molecular



weight 68,800, and that when this correction is made for the filtration of hemoglobin, its reabsorption mechanism is limited by a maximal rate of transfer (see below). The data upon which the second of these considerations was based are open to an alternative interpretation. It is probable that circulating hemoglobin exists as an equilibrium mixture of molecular species with one, two, three, or four equivalents of iron, rather than as the 68,800 species alone. The filtration of hemoglobin under this circumstance would have the proportion of low molecular weight hemoglobin as its limiting factor rather than the number of membrane pores which can be traversed by a protein molecule of molecular weight 68,800. The reversible nature of such an association and dissociation and the low concentration of dissociated hemoglobin required by these data would make the direct demonstration of the latter difficult.

*Renal blood flow.*—The measurement of renal blood flow by excretion studies has been placed upon a firmer experimental basis. It has been demonstrated that the *p*-hydroxy, *p*-amino, and *p*-acetyl amino derivatives of hippuric acid have clearances at low plasma concentrations which are identical with those of diodrast and hippuran in the normal dog (11). This supports the belief that the limitation in the excretion of these substances lies in the mechanics of blood and fluid distribution within the kidney rather than in diffusion or, at low plasma concentrations, in the transfer mechanism. The degree to which the plasma clearances of these substances approximate the plasma flow to excretory tissue has not been finally settled (12, 13), but it seems likely that the two are quite close in the normal animal. The use of the diodrast clearance for this measurement in clinical medicine has been simplified by improvements in its chemical determination (14) and by the demonstration that satisfactory plasma concentrations are obtained after subcutaneous injections (6).

*Tubular reabsorption and tubular excretion.*—Considerable simplification was achieved in the evaluation of renal transfer systems by the demonstration that in general they are limited by a maximal rate of tubular transfer, at least insofar as organic substances are concerned. This maximal rate, or *T<sub>m</sub>*, is expressed in milligrams per minute and may apply to processes of tubular reabsorption or tubular excretion. It represents the maximal capacity of the renal tubule cells to actively transport a given substance and is independent of the amount of the substance presented or its concentra-



tion, provided these are adequate. These circumstances have permitted its use as a functional measurement of the amount of renal tubular tissue. A maximal rate for tubular reabsorption was first established for glucose in the dog and has since been described for ascorbic acid in the dog (15) and man (cf. 16), glucose in the frog (17) and in man (18), and hemoglobin (10) and inorganic phosphate (19) in the dog. Transfer maxima for processes of tubular excretion are numerous; these now include creatinine in the dog-fish (20) and phenol red in the frog (21). Studies on the reabsorption of the nutritionally essential amino acids are less definitive in nature. The reabsorption of these is by an active process, and, as might be expected, each amino acid has its own specific rate of transfer (22, 23).

The demonstration that the tubular reabsorption of inorganic phosphate is limited by a maximal rate is particularly interesting since it is the second inorganic electrolyte which, under certain circumstances, manifests a limitation of this type; the other is sulphate. The changes in plasma phosphate in this study were acutely superimposed upon an otherwise normal electrolyte pattern, as were the observations with sulphate when this system was examined (cf. 24). A maximal rate of a given absolute value should be accepted for these substances with some caution. It is known that a relationship exists between the excretion and presumably the reabsorption of any one ion and the concentrations of the others in the plasma and tubular fluid, and it is to be expected that a change in the electrolyte composition of the plasma other than the specific ion under observation, i.e., phosphate or sulphate, will change the quantitative relationships of the reabsorptive system. The demonstration that phosphate  $T_m$  is increased by vitamin D and decreased by parathormone is particularly interesting as is the suggestion that the antirachitic action of the vitamin may be due to this action.

The tubular system responsible for glucose transfer has received further attention during the past year. Experiments on the frog (17) support the belief that absolute glucose concentrations in plasma, glomerular and tubular fluid are important only insofar as they determine in part the quantity of glucose delivered to the reabsorptive surface. Observations in the dog (25) demonstrate that relatively few precautions need be followed for valid measurements of glucose  $T_m$  provided the animal is well hydrated and the arterial



plasma glucose is maintained at an adequate and fairly constant value. Under these conditions the system in the dog has surprising stability, and the glucose  $T_m$  of any animal is quite constant over a period of many months. Excessive insulin may acutely depress it, but it is not affected by epinephrine nor by marked changes in dietary regime, and it is not related to the concurrent rate of glomerular filtration. For these reasons it is advanced as an excellent means for the quantitative characterization of renal tubular function.

Studies have been continued on the enzyme or carrier system in the tubule cells by which glucose is transferred from the lumen to interstitial fluid. These support the view that a phosphorylation of glucose, which is catalyzed by a specific enzyme, kidney phosphorylase, occurs in the course of tubular reabsorption and that alkaline phosphatase is concerned with the dephosphorylation of the hexosephosphoric acid ester. It seems likely that phlorhizin inhibits glucose reabsorption by blocking some phase in the action of kidney phosphorylase on glucose (26, 27, 28, 29, 30, 31). There exists a distinct possibility that the cellular limitation which results in a maximal rate of transfer may be derived from this portion of the transfer system. Preliminary experiments on the otherwise normal dog suggest that phlorhizin may inhibit the active tubular reabsorption of glucose by entering into competition with glucose for the transport mechanism and by displacing glucose from it in much the same way that glucose can exclude xylose (32). The kinetics of this apparent competition are worthy of further study, particularly since it may permit the bridging of the gap between studies of this mechanism *in vivo* and *in vitro*.

A second consideration is emphasized by experiments which demonstrate that phlorhizin lowers the transfer maximum of diodrast (33) and probably of ascorbic acid (34). This somewhat diverse effect may indicate that phlorhizin has a more diffuse effect upon the renal cell than is suggested in the studies on glucose transfer, perhaps through an effect upon the energetics of cellular metabolism.

There has been no further clarification of the cellular mechanism by which a specific limitation is placed on the rate of renal tubular transfer of a given substance. However, the data on the tubular excretion of creatinine in the dogfish (20) and phenol red in the frog (21) and the tubular reabsorption of ascorbic acid in the



dog (15) and man (16) are in keeping with that of previous studies on the kinetics of these processes.

Additional information has accumulated on the ability of various dyestuffs to participate in processes of tubular excretion in the perfused kidney of the frog. Such participation, with certain exceptions, would seem to depend largely upon a polar-nonpolar molecular configuration (35, 36, 37, 38). It has been concluded that this polarity is essential for the proper orientation of the molecule on the cell surface, and that in this group of substances this initial orientation is essential for active transfer. It would be hazardous to extend this concept beyond the specific groups of substances which have been studied or perhaps to substances of similar molecular complexity. Certainly the renal transfer of such substances as urea in the frog and creatinine or creatine in many vertebrates cannot be considered from this standpoint. It is probable, furthermore, that the situation is considerably more complex than this, even in the initial stage of the process which involves the entry of the substance into the active cell. The ability of phenol red to enter the cells of the chick mesonephros in tissue culture has been shown to depend upon the maintenance of a normal polarity of the cells themselves (39). This polarity obtains when the cells are grouped so that an organized structure with a lumen can be formed. If this arrangement is lost due to tearing with micromanipulation needles, or by dissolving the intercellular cement substance with solutions low in calcium, the cells which separate round up, and there is a dissolution of the brush border and the underlying protoplasmic organization. Accompanying this structural change, the cell membrane becomes wholly impermeable to phenol red, whereas previously it was completely permeable as evidenced by the relationship between intra- and extracellular dye concentration. These changes are wholly reversible. It may be inferred from this that the membrane of the tubular cells cannot be considered apart from the organization of the active transfer mechanism within the cell since the latter donates specific properties to the cell membrane which condition the ability of material to traverse it. The importance of the physicochemical structure of a molecule with respect to its ability to participate in this type of mechanism should not be minimized. However, the properties dependent upon this may not exert their influence in a specific fashion at the cell surface



but at some active interface within the cell which is a component part of the mechanism of transfer.

It is well known that certain specific renal tubular functions are controlled by the endocrine system, i.e., reabsorption of water, sodium, etc. However, the stability of the transfer maxima which have been described for many organic substances has carried the suggestion that many processes of renal tubular transfer may operate in a more or less autonomous fashion. The recent demonstration that complete hypophysectomy reduces the ability of the dog kidney to transfer diodrast (40, 41) is strong evidence opposing this concept. The potential role of the endocrine system in the control of renal tubular function is further emphasized by the demonstrations that a variety of the sex and adrenal cortical hormones and their derivatives increase renal mass if given in adequate amounts (42, 43, 44) and that the compensatory hypertrophy which usually follows unilateral nephrectomy is enhanced by testosterone (45) but does not occur in the absence of the anterior pituitary (46, 47). These findings are particularly interesting in view of the relationships between anterior pituitary function and the normal liberation of the sex hormones, between anterior pituitary and adrenal cortical function in the regulation of protein metabolism, and in view of the hypertrophic effect of dietary protein on renal mass and upon the rate and extent of compensatory hypertrophy following unilateral nephrectomy. Correlative anatomical and functional studies are obviously indicated.

#### THE INTERRELATIONS OF DISCRETE RENAL PROCESSES

Considerable clarification of the functional organization of the kidney has resulted from the simultaneous measurement of a series of discrete processes. It has been demonstrated that the marked variations in renal blood flow found in any series of supposedly normal individuals is correlated with parallel variations in the functional renal mass (i.e., diodrast or glucose  $Tm$ ) of the individuals in the series (48). This correlation permits the establishment of more rational standards for the study of this function in the diseased kidney. In this situation information on the renal blood flow may be of little value if at the same time there is no knowledge of the amount of tissue to which the blood is distributed (49, 50, 51, 52). Other studies have established the value of simul-



taneous measurements of renal blood flow and glomerular filtration rate. This procedure, together with other considerations, permits a tentative evaluation of changes in the tonus of the afferent and efferent arterioles (53, 54, 55). The use of such combined measurements is given specific point by the observations that at least in dog (25), and probably in man (18), all the nephrons are continuously active. The functional evidence for this is particularly strong in the normal dog and is supported by previous anatomical studies. This consists of the demonstration that changes in glomerular filtration rate in the well-hydrated animal are superimposed upon a constant mass of reabsorptive tissue as demonstrated by a constant glucose  $Tm$  (25). Furthermore, the drastic expansion of the circulation by excessive amounts of intravenous glucose (25) or saline (56) solution does not increase glucose  $Tm$  over the control value, while it may dramatically elevate the glomerular filtration rate. It follows from this that changes in the glomerular filtration rate in the well-hydrated dog result from changes in the filtration pressure of the entire filtering bed rather than from changes in the proportion of total nephrons which are active; also, that changes in renal blood flow result from variations in the resistance in the entire renal vascular bed rather than from an increase or decrease in the number of open vascular channels. It seems likely that a similar situation obtains in normal man (18).

When glucose reabsorption is studied in the normal dog with progressive increments in the plasma arterial glucose concentration, the plasma level at which frank glycosuria appears is essentially the same as that at which glucose  $Tm$ , or the complete saturation of all the nephrons, is reached. It is essential for this result that the capacity of each glomerulus to filter be closely adjusted to the capacity of its dependent proximal tubule to reabsorb glucose; otherwise the glucose concentration in plasma and hence in glomerular fluid at which all the tubules are just saturated would be different. This circumstance indicates that although the length of the proximal tubules and the size of the glomeruli vary considerably in the dog, the variation of one is not independent of the other when considered as component parts of individual nephrons (25). This relationship carries important consequences with respect to control of water and electrolyte balance (see below) and has found ingenious application in the evaluation of glomerular activity in man (18). It has been suggested that if glucose reabsorption and



excretion are observed on slowly rising blood concentrations, it is possible to measure the dispersion in the activity of glomeruli with respect to the reabsorptive capacity of their attached tubules: the higher the filtration rate of any glomerulus in relation to the ability of its tubule to reabsorb glucose, the lower the plasma glucose concentration which is necessary to saturate the reabsorptive capacity of its tubule. It follows from this that the relationship between the lowest plasma concentration at which frank glycosuria occurs and that at which glucose  $T_m$  is reached is an indication of this dispersion. Glomerular activity, so measured in normal man, varies from 0.66 to 1.33 of the mean for all glomeruli. The extension of this concept to the diseased kidney or to functional changes in the normal kidney will make available an additional and important datum to aid in the analysis of the functional organization of that situation.

Glomerular activity in its broadest sense is capable of drastic variation through many variables, both physiological and pharmacological in nature. These changes are due primarily to variations in the systemic blood pressure or to the resistance offered at the afferent and efferent arterioles. The glomerulus is so situated between these arterioles that a change in arteriolar resistance must be considered from the standpoint of its consequences on glomerular pressure and hence on glomerular filtration rate, as well as its effect upon renal blood flow. This has received critical examination, and certain relationships have been derived which relate the physical factors concerned; i.e., mean arterial pressure, glomerular and intrarenal pressure, colloid osmotic pressure of plasma, afferent and efferent tone or resistance, glomerular filtration rate, and renal blood flow (53, 54, 55). Some of these are directly measurable, other indirectly (57), while values for others must be assumed.

The initial analysis of this situation (55) followed the observation that glomerular filtration rate in man remains constant when the renal blood flow is changed by epinephrine or pyrogenic material. It was concluded that the renal action of these substances was on the efferent arterioles since in theory a change in efferent tone would produce an inverse change in renal blood flow and the filtration fraction, with the glomerular filtration rate remaining constant; whereas changes in afferent arteriolar tone would cause all three variables, i.e., glomerular filtration rate, renal blood flow,



and the filtration fraction, to move in the same direction. A subsequent treatment (53, 54) led to much the same conclusion with respect to the effect of changes in the afferent arterioles but to quite different predictions in the case of changes on the efferent side. It was stated that as the resistance in the efferent arteriole is progressively decreased, the afferent resistance remaining constant, filtration rate rises from zero to a maximal rate and subsequently decreases to zero as a hyperbolic function of the renal blood flow.

It is not within the province of this review to examine these conflicting views in detail. However, the importance of the concepts developed demands more than casual mention. The necessity for assuming absolute values for certain variables which at present are unmeasurable weakens the forcefulness of any mathematical statement of these relationships. This is particularly true in the case of the intrarenal pressures. It is quite likely that changes in renal blood flow are accompanied by changes in these pressures which are not the same in the case of afferent variation as in efferent variation. The forces across the glomerular membrane are so balanced (53, 54, 55) that small absolute changes in these pressures will result in proportionately larger changes in the filtration fraction. More specifically, no limiting factors were introduced in the initial treatment (55) which would permit a valid description of the system at all pressures and all flows, while in the latter treatment (53, 54), variations in renal blood flow and glomerular filtration rate were treated on the basis of a fixed resistance for one or the other arteriole. This method cannot be applied to elastic resistances since in these the absolute magnitude of the resistance changes with the internal pressure, and in the glomerular apparatus the pressure in one arteriole will always depend in part upon the state of tonus of the other arteriole. Furthermore, this form of treatment (53, 54) does not recognize the resistance offered in the glomerular capillaries which becomes proportionately large as the resistance in the efferent arteriole approaches zero. Under this circumstance filtration will proceed at the expense of the pressure developed by this resistance. The glomerular filtration rate cannot in theory, or in practice, approach zero at high renal blood flows as predicted in this treatment. If corrective factors were introduced into the equations of each of these hypotheses, they would diminish to a considerable extent the differences in their quantitative implications.



An appreciation of the general pressure-flow relationships in the glomerular system is essential for an understanding of the regulation of renal activity, and while the equations describing this system do not agree and may not be precise statements of the system, the studies themselves (cf. 55) have clarified to a considerable extent the factors concerned with this regulation. A difficulty which must be considered in the final analysis is the presence of a certain amount of autonomy in the renal vascular bed. This has been demonstrated by experiments in which the pressure in the renal artery was altered (cf. 58). One would infer from this circumstance that changes in the caliber of one set of the arterioles at constant arterial pressure would result in some physiological adjustment of the other since it is unlikely that a change in arterial pressure per se is the primary factor which throws this autonomous mechanism into action. If this is the case in fact, the change of a single set of arterioles is an unlikely physiological or pharmacological event.

Glomerular filtration rate and renal blood flow have been studied together in the rabbit (59), in the seal (60), and in the hypophysectomized dog as compared to the normal (40, 41, 61). In the rabbit hydration leads to an increase in both these variables to essentially the same extent so that a relationship obtains between filtration rate and urine flow. In the seal filtration rate and renal blood flow are maintained at very low values during fasting but increase reversibly within a few hours after feeding; the increase of one is in direct proportion to the other so that a constant filtration fraction is maintained over the entire range. It has been noted above that complete hypophysectomy drastically lowers diodrast  $T_m$  in the dog. This change is accompanied by a proportional lowering in filtration rate and renal blood flow (40, 41, 61). The changes in all three of these situations must involve the participation of both sets of arterioles (53, 54, 55). However, the quantitative contribution of each cannot be determined at present.

These combined techniques should clarify many of the problems presented by the diseased kidney. Although certain objections have been raised to their use under these circumstances (62), these objections stem largely from an improper understanding of their advantages and disadvantages (52). Unanswered as yet is the question of the functional control of the mechanisms of active transfer upon which the measurements of functional renal mass and effective renal blood flow depend. If these tubular mechanisms



are influenced extensively by the endocrines, the quantitative relationship between active tubular tissue and its functional evaluation would be capable of variation. Similarly, if these mechanisms can be impaired by a disease process or functional derangement without loss of cellular substance, the relation between actual plasma flow to tubular tissue and that calculated by the diodrast clearance would be altered from the normal. An example of the latter is seen in the case of the action of phlorhizin (33).

#### THE EXCRETION OF WATER AND ELECTROLYTES<sup>2</sup>

This phase of renal physiology derives its primary importance from the fact that the excretion of water and electrolytes, together with their ingestion and absorption, directly determines the volume and electrolyte composition of extracellular fluid and through this influences the composition of the cells themselves. The integration of the discrete processes, which together determine this renal excretion, is beginning to resolve into a fairly definitive picture. It is unfortunate, however, that the information on many of the more complex experimental situations is insufficient to permit examination in the light of these advances. The studies to date have been largely confined to the mammalian kidney, so unless stated to the contrary, the investigations detailed here relate to this class of vertebrates.

*Functional anatomy of the nephron.*—Considerable simplification has been achieved by the demonstration that at least in the dog (25), and probably in man (18), all the nephrons are continuously active and, furthermore, that the reabsorptive capacities of the tubules of the individual nephrons are closely correlated with the ability of their attached glomeruli to filter (25). These circumstances permit the operations of the normal kidney to be examined as if they were occurring in a single nephron. This approach may be subject to slight modification in the future but is amply justified for our present purposes. It is axiomatic that the reabsorptive burden presented to the tubule is quantitatively determined by composition and rate of formation of glomerular filtrate. The initial tubular contribution in the determination of water and electrolyte

<sup>2</sup> The viewpoint developed in this section is partly the result of work which has been completed in this laboratory but which is not published at the time of this writing (cf. 65). It has been necessary to draw on some of this unpublished information in order to present a valid description of this phase of the subject.



excretion consists of the active withdrawal of sodium and chloride as well as other osmotically active material by the proximal tubule. This was demonstrated in the mammalian nephron by analyses of fluid obtained by direct puncture of discrete nephrons with subsequent identification of the site of puncture. It was also established that extensive reabsorption of water occurs in the proximal tubule and that this takes place in the absence of a measurable increase in osmotic pressure (63, 64). These findings are in keeping with previous deductions on the happenings in the proximal tubule and with the high correlation which obtains between water reabsorption and chloride reabsorption in the normal dog (56) when the urine flow is so high that distal function is quantitatively unimportant. In terms of mechanism it may be suggested that the active withdrawal of electrolyte and other osmotically active substances by the proximal tubule cells establishes a diffusion gradient for water, and that this results in its passive reabsorption in both the proximal segment and Henle's loop. It is unlikely that this passive process always keeps pace with the active reabsorption of solute in the normal animal as was the case in the experiments involving renal tubular puncture (63, 64); otherwise, a hypotonic urine would not result when distal function is suppressed (e.g., water diuresis). Water reabsorption then continues in the distal segment due to the incomplete dissipation of its diffusion gradient proximally and due to an active process which requires energy and only proceeds efficiently in the presence of the antidiuretic hormone. The amount and composition of the fluid delivered to the distal segment will be determined by the balance existing between the reabsorptive capacities of the proximal segment and the quantity of water and osmotically active material filtered at the glomerulus. It is inherent in this view that the proximal and distal portions of the nephron are so related that variations in function proximally, i.e., glomerular and proximal tubular, are potential factors in the determination of the volume and composition of urine through their effect upon the volume and composition of fluid delivered to the distal segment (65).<sup>3</sup>

<sup>3</sup> Additional information has been made available on the site (195) and mechanism (195, 196) of ammonia formation and the related subject of acidification of the urine (197, 198, 199, 200). These functions are primarily or exclusively located in the distal portions of the amphibian nephron, and it seems likely that this is also true in the mammalian nephron.



The large order of magnitude of the water reabsorbed in the mammalian nephron introduces an added variable which, though external to the nephron, is potentially a factor in determining the extent of water reabsorption. The kidneys of the normal adult man weigh approximately 300 gm. and reabsorb water at the rate of about 125 cc. per min. This must result in, or requires, an active circulation of interstitial fluid, and there is ample evidence that this is present in the normal kidney. An impairment in this circulation or in the prompt return of this fluid to the intravascular renal space would drastically influence the physical forces which result in the progress of water across the renal tubule. This would directly affect that moiety of water which is reabsorbed proximally by a passive process and would indirectly influence the active process in the distal segment by changing the amount and perhaps the composition of the fluid delivered to it. The diuresis which results from the dilution of plasma protein in the perfused kidney and in the anesthetized dog, and which in the latter occurs without an increase in glomerular filtration rate, may be attributed to this portion of the system rather than to a direct tubular effect as has been suggested (66). Unfortunately, there is no simple means of evaluating the importance of this aspect of the system at the present time.

The physiological control of these tubular processes is humoral in nature, and the renal nerves are mentioned only to dismiss them as normally unimportant factors (67). The occurrence of polyuria after drastic neurological injury, such as spinal cord destruction (68), does not affect this decision. The extent of sodium reabsorption in the proximal tubule depends in part upon the presence or amount of adrenal cortical hormone. This hormone and others chemically related to it (69, 70, 71, 72, 73) enhance the ability of this segment to actively reabsorb sodium while the antidiuretic hormone of the posterior pituitary has a depressive action on this process. The physiological importance of the latter action and the integration of the two actions in the control of sodium metabolism (74) are open to some question since the experimental work upon which such integration is suggested has made use of unphysiologically large amounts of the active principles. The active reabsorption of water in the distal segment is undoubtedly under the control of the antidiuretic hormone of the posterior pituitary although it cannot be concluded that this process proceeds only in the presence of this principle.



*Antidiuretic hormone.*—An interesting examination has been made of the antidiuretic hormone content of the pituitary glands of the various classes of vertebrates (75). It was demonstrated that, per gram of tissue, the pituitaries of mammals characteristically contained eight or more times the amount of antidiuretic hormone found in the pituitaries of any of the other classes. However, this fact, taken in conjunction with the specific action of the hormone and the full development of Henle's loop in the mammal, is not sufficient to assign the process of hypertonic water reabsorption to this portion of the nephron. It does not seem reasonable to allocate an essential function to a segment of the nephron which is not present in all nephrons of a given kidney. As this seems to be true for the loop of Henle, or at least for the thin portion, judgment on this question must be withheld.

The geographical extent of the tissue giving rise to the antidiuretic hormone is not as yet clearly defined. Retrograde degeneration of essentially all the cells of the supraoptic and paraventricular nuclei follows the ablation of the entire neurohypophysis (76) as well as section of the connecting pathways (77) in the dog, and there is a semiquantitative relationship between the extent of this retrograde degeneration and the severity of the resulting polyuria (77, 78). These findings, taken together with the demonstration that the nuclei themselves do not contain the active principle (77), support the belief that the origin of the antidiuretic hormone is limited to the neurohypophysis and that the control of its liberation normally involves this entire system. The possibility remains, however, that in some species or in certain individuals in a given species this tissue may have a more diffuse extension into the hypothalamus than is commonly observed (79). Complete agreement has not been reached on the anatomical changes in the pars nervosa which are related to variations in the state of hydration of the animal (80, 81). It does seem clear, however, that states of dehydration are characterized by the progressive depletion of the active principle whereas hydration permits its reaccumulation (81).

The concentration of the hormone is too low in peripheral blood for its functional demonstration by the injection of blood from normal dehydrated dogs into dogs with diabetes insipidus (82). This finding is in keeping with low rate of hormone administration which will maintain antidiuresis and which presumably is close to the normal rate of hormone liberation (65). The range of



dosage by constant intravenous infusion which produces this effect in a moderately sized dog (15 kilos) is 1.0 to 5.0 milliunits per hour. This may seem surprisingly small when compared to the amounts commonly used in physiological investigations but is in keeping with the effectiveness of pituitary preparations whose rate of absorption from the subcutaneous tissues has been considerably diminished (83, 84). There seems to be no question that the urine of the normal but dehydrated dog contains one or more anti-diuretic substances, but these may have diverse origins within the body (85, 86). Certain functional observations suggest a pituitary origin (82), but other evidence (85, 86) indicates that at least a portion of the active urinary material arises elsewhere. It is clear that the kidney can excrete the antidiuretic hormone. However, this information is relatively unimportant until it has also been shown that the administration of the hormone to an animal with diabetes insipidus in normal physiological amounts is accompanied by its renal excretion in demonstrable amounts. The absence of an antidiuretic substance in the urine of the dog with diabetes insipidus after two to four days of dehydration (82) may be due to the drastic physiological consequences of the resulting dehydration rather than the absence of a functioning pars nervosa. It must be concluded then that there has been no clear demonstration of the normal renal excretion of posterior pituitary antidiuretic hormone. However, this does not seem to be an essential datum in the establishment of the function of this hormone in the control of mammalian water and electrolyte balance.

The dual role which may be assigned to the antidiuretic hormone, i.e., the impairment of sodium reabsorption in the proximal and the enhancement of water reabsorption in the distal tubule, permits what superficially would seem to be diametrically opposed results. Thus in properly prepared animals, large amounts of the hormone can result in an increase in urine flow (65) even though the normal or characteristic action is antidiuretic in character (87). This increase in urine flow does not reach diuretic proportions, occurs with no change in glomerular filtration rate, and may be attributed to the less complete reabsorption of sodium in the proximal tubule. This action of the hormone may be expected to be a factor in determining the degree of antidiuresis at any dosage level of hormone administration and in any physiological condition. It would become increasingly effective as the reabsorptive burden on the sodium system is increased, as by an increase in glomerular filtra-



tion rate. Similarly, the cessation of hormone liberation which results from hydration permits the more complete reabsorption of sodium. Such an effect proximally, taken in conjunction with the suppression of active tubular reabsorption of water distally, permits the nephron to discard water while retaining sodium. The dual action derives specific importance from the definite, though small, increase in glomerular filtration rate which follows the administration of a large amount of water. The increase in the filtration of sodium would result in the loss of considerable quantities if at the same time its reabsorption were not enhanced. The reverse of this may be expected during periods of dehydration, permitting sodium to be discarded at least in proportion to the excretion of water until there is a contraction in glomerular filtration rate and hence in the filtration of sodium. It is obvious from these considerations that the effect of the antidiuretic hormone upon the sodium system is subject to acute variation and that this must be superimposed upon the more stable action of the adrenal cortical hormone. It is not necessarily integrated with the latter in the true sense. The experiments used to support such "integration" (74, 88, 89) demonstrate nothing more than an action by two hormones upon a single mechanism.

It is obvious from the above that many factors other than the antidiuretic hormone operate in determining the rate of water excretion and that with our present information on many of these factors the mechanisms involved cannot be clarified (90, 91). Nevertheless, it is difficult to fit into such a system, however complex, the acquisition of a tolerance to small doses of the hormone (92, 93). These experiments are not too convincing, and one suspects that uncontrolled variables have conditioned the results in some manner.

*Adrenal cortical hormone.*—Little can be deduced from the experimental work on the renal action of this hormone other than that in general (cf. 73) it and certain chemically related substances have a sodium-retaining action, and that presumably this action is exerted on the active reabsorptive process in the proximal segment. This deficiency in information is largely due to the common use of small laboratory animals in the experiments with these substances; this, in turn, necessitates the application of relatively nonspecific criteria to evaluate the effectiveness of substances on what appears to be a highly specific function. Of the substances related to corticosterone and its esters (72), desoxycorticosterone



acetate and progesterone are particularly active in the retention of sodium (70, 94), more so than the cortical hormone itself. Their effectiveness in severe cortical insufficiency and the time relationships of the action are too complex for present analysis (69) as are the refractoriness which results from the continued administration of cortical "sodium factor" (70, 71) and the cortical atrophy produced by progesterone (95) and desoxycorticosterone (96). The complete absence of information on the normal rate of liberation of the cortical hormone is a barrier to evaluation of the physiological importance of these findings.

*Over-all water and electrolyte balance.*—A variety of experimental preparations have been used in the attempt to define grossly the control of water and electrolyte balance. Unfortunately, in most instances, these studies do not contain an experimental definition of the variables which are necessary for a clarification of the renal mechanisms involved. In this category come experiments which demonstrate a relationship between the ingestion of saline solution (97) and nitrogen-containing food (98) and the severity of the polyuria in diabetes insipidus, those which demonstrate that excess amounts of desoxycorticosterone produce a polyuria in the normal dog which is enhanced by the addition of salt to the diet (99), those which demonstrate that the cortical hormone or its allied substances (74) and anterior pituitary extracts (88) enhance the severity of the polyuria in diabetes insipidus, and those which seek to obtain a normal water and electrolyte balance by the combined administration of cortical and posterior pituitary substances (74) or which seek to examine one deficiency superimposed upon the other (100). Equally difficult is the problem of placing the thyroid and its secretions in the mechanisms which control water balance (101, 102, 103, 104), particularly in view of the general metabolic action of this endocrine gland. It is in keeping with expectation that when a deficiency exists in one or another of the factors which normally control water and electrolyte balance, a normal internal environment can only be maintained under the most favorable conditions (105, 106). Similarly, when the internal environment itself has been drastically altered, diverse effects which are not amenable to simple analysis (107, 108, 109) are to be expected in the effector organ of the system.

Investigations have been initiated on the renal control of water and electrolyte balance in the newborn. While this portion of the subject is in its early stages of development, certain important



features are already clear. The glomerular filtration rate is lower in the newborn than in the adult when compared on a basis of surface area (7, 110), and the low urea, sodium, and potassium clearances may be related to this finding (110). The newborn does not react to the ingestion of water by a prompt diuresis but acquires this ability in the early weeks of infancy (111). This also may be related to the low initial rate of glomerular filtration and to its rapid increase during the first few weeks of life. It seems likely that the incomplete elaboration of the glomerular membrane in the otherwise completely formed nephron is the anatomical basis for many of these results (112, cf. 113, 114). In any case, it must be accepted that the functional potentialities of the kidney in the newborn are limited as compared to the adult (110). This feature, together with the large daily turnover of water and electrolyte in proportion to the water and electrolyte content of the body, leads to a high degree of physiological instability.

#### EXPERIMENTAL HYPERTENSION

This has been one of the more active fields of investigation since the initial demonstration that a sustained hypertension may result from an impairment of the renal circulation. The studies generating from this original contribution have progressively invaded the various fields of physiology so that the renal aspects of the subject make up only a small portion of the whole. During the past year this aspect of the work has been largely a continuation of lines of investigation previously initiated. The more important contributions relate to a further analysis of the factors which result in the liberation of renal pressor material, a consideration of the humoral agents involved, a study of the consequences to renal function of a limitation on the renal blood supply or of an excess of circulating pressor or antipressor substances of renal origin. Metabolic studies have been initiated which seek to define the conditions under which the kidneys give rise to pressor agents from specific but inactive substrate. Finally, extensive observations have been made available on the status of renal function in the essential hypertension of man.

*Experimental material.*—The methods used for the production of experimental hypertension remain the same as those used previously. These are mechanical interference with the renal circulation by renal arterial clamps (115) and by the induction of a perinephritis with cellophane (116), unilateral renal injury (117), and



in some species, ablation of renal tissue. It has been demonstrated that although transient hypertension may result from intermittent renal arterial obstruction (118) or from partial occlusion of the renal vein (119), neither of these produces a permanent elevation in blood pressure. These studies suggest that sustained hypertension does not result from temporary ischemia or repeated temporary ischemia such as might be caused by recurrent and excessive vasomotor activity. This view is fortified by the demonstration that if a chronic renal ischemia is relieved by the establishment of an adequate collateral circulation, the elevation of systemic blood pressure may be quickly reduced (120). A temporary hypertension results when the circulation is restored in a previously completely ischemic kidney in the cat, the dog, and the rat (121, 122), while similar ischemia of other organs does not produce this result. It is interesting in this relation to note that this type of ischemia does not produce a transient hypertension in the rabbit although chronic impairment of the renal circulation or transplantation of an ischemic kidney into a nephrectomized animal produces the usual result (123). Superficially it would seem that the hypertension and attendant renal ischemia which result in certain individuals on attaining the erect posture may be classified with the situations that give rise to a temporary hypertension (124). However, it is not clear whether the changes in glomerular dynamics which accompany the renal ischemia in this condition contribute to the liberation of pressor material by their effect upon renal blood flow, or are wholly secondary.

Observations on renal blood flow in the dog before and after the application of arterial clamps demonstrate that there may be little permanent change in the renal blood flow (58, 125). It is suggested that arterial constriction may be effective because of the reduction in pulse pressure rather than an absolute reduction in the renal blood flow (125, 126). An organ such as the kidney with an elastic capsule and an extraordinarily high turnover of interstitial fluid (see p. 310) may well depend upon arterial pulsations to maintain an adequate circulation of this fluid, and the distribution of essential solute to all the renal cells may depend in part upon this circulation. A reduction in the pulsations of the organ would undoubtedly diminish the efficiency of this renal interstitial fluid circulation and would be equivalent to a reduction in the efficiency of the renal circulation itself.

Mechanical interference with the renal blood supply is accom-



panied by certain morphological changes in renal tissue. Acute complete ischemia is shortly followed by progressive changes in the mitochondrial apparatus of the proximal tubule cells (127). The more chronic impairment is accompanied by the progressive differentiation of the afibrillar cells in the juxtaglomerular apparatus. These undergo hypertrophy and hyperplasia with an increase in their granularity (116, 128). It has been suggested that this anatomical change may be related functionally to the liberation of renin by these kidneys and that the afibrillar cells, and more specifically their granules, are the origin of this material (128). This possibility cannot be denied, but at present it is based entirely upon conjecture (116).

*Pressor substances.*—It is definitely established that a substance called renin and having potential pressor activity is extractable from the mammalian kidney. Two difficulties arise in the interpretation of experiments which are dependent upon the bioassay of this material. The technique of bioassay has not been particularly well standardized (126, 129, 130, 131, 132), so the results of different investigators are difficult to compare on a quantitative basis. Perhaps more important is the fact that the amount of pressor material in a kidney extract, or its apparent concentration, depends upon the care of the tissue prior to its preparation, the method of preparation used, and the duration of time between the preparation of the extract and its assay on a test animal (129, 132). Kidneys prepared by rapid freezing and desiccation while frozen yield extracts which in many instances have negligible pressor activity; however, if such inactive freshly prepared extracts are allowed to stand, they may progressively develop a well-marked pressor action. These difficulties somewhat weaken the significance of the correlations which have been attempted between the renin content of a kidney and the physiological state of the organ (133, 134) or of the animal prior to extirpation (126). In any case, generalizations do not seem to be permissible. For example, freshly prepared extracts of ischemic kidneys of dogs usually have a greater pressor activity than similar extracts of normal kidneys, but the converse of this is true in the rat. However, in both the dog and the rat, extracts of ischemic kidneys progressively increase in pressor activity on standing while those of normal kidneys decrease progressively (132).

There is little additional information on the chemical nature of renin. It is a protein, a protein-like substance, or contains protein



as a constant contaminant even in the purest preparations. It has well-marked antigenic properties although the development of a high precipitin titer does not diminish the physiological response (135). It may be in consequence of its antigenic properties that the repeated injection of heterologous renin results in the production of an antirenin and may effect a temporary reduction of experimentally produced hypertensions (136, 137, 138).

The transient hypertension which follows acute complete renal ischemia (121, 122) appears to be due to an increased rate of formation or liberation of renin (139) or perhaps a renin-like substance (140), which is distributed to the systemic circulation on the re-establishment of the renal blood supply (141) or which can be recovered in the perfusates of the kidney after extirpation (139). The presence of renin or a renin-like substance in the perfusates of completely ischemic kidneys is presumably due to an exaggeration of the effect which results in the liberation of an excess of pressor material in the venous outflow of kidneys where there is a mechanical impairment of the renal blood supply (140, 142, 143, 144, 145). The demonstration of this in the latter preparations has been indirect but quite convincing, at least insofar as the dog is concerned. The liberation of a pressor substance is so rapid in the animal with ischemic kidneys (146, 147) and in essential hypertension (146, 148) that the systemic blood attains demonstrable pressor (i.e., vasoconstrictor) activity. A difficulty which attended this demonstration in the past was the presence of normal functioning kidneys in the test animal (149, 150). These diminish the effectiveness of this type of material by destroying the pressor substance or by the liberation of inhibitors (126, 129, 149, 150, 151).

Many substances have been assigned a role in the mechanism of the pressor action initiated by the injection of renin or by the impairment of the renal circulation, but these will not be reviewed in detail (cf. 126, 129). It is important to note that renin is not itself a pressor substance; rather, the reaction between renin and renin activator results in a specific crystalline substance which has been called angiotonin or hypertensin (126, 152, 153, 154, 155). The pseudoglobulin fraction of the plasma proteins seems to be the substrate from which angiotonin, the pressor agent, is derived by the enzymatic action of renin (126, 155, 156). It has been suggested that angiotonin is the specific substance which causes the increased tonus in the smooth muscle of the arteriolar system



which in turn produces the increased peripheral resistance characteristic of experimental and essential (126) hypertension.

*Antipressor substances.*—Accepting a humoral mechanism for the causation of experimental hypertension of the renal type, two lines of investigation, predicated on different viewpoints, are being prosecuted: (a) The kidney under certain pathological conditions may produce a substance which, liberated into the circulation, gives rise to hypertension (cf. 126); (b) the kidney normally may produce an essential substance, the absence of which from the organism results in hypertension (129). From either viewpoint there is considerable evidence that the kidney liberates or contains a substance capable of inhibiting the pressor principle angiotonin and, in accordance with the first premise, the renal pressor material liberated in experimental hypertension of the renal type (cf. 157, 158, 159). The logical extension of each line of investigation has led to the independent isolation of a material from kidney substance which is capable of lowering the systemic blood pressure in a variety of types of experimental renal hypertension and in essential hypertension in man and which in similar amounts does not affect the blood pressure in the normal animal (126, 129, 151, 157, 158, 160, 161). The demonstration of an angiotonin inhibitor in blood leaving the normal but not the ischemic kidney (162) and the antipressor effect of normal blood in experimental hypertension (163) can be contained in either thesis.

It has been shown that the parenteral injection of tyrosinase, a phenol oxidase, reduces blood pressure in experimental hypertension and in the essential hypertension of man (164, 165). However, it has not been established that this depression is a direct result of the specific action of the enzyme.

*Metabolic considerations.*<sup>4</sup>—The above studies consider the kidney as the site of formation or destruction of specific substances as if the system of blood and kidney were more or less self-contained. Obviously, this is not the case (cf. 126, 129). The participation of the endocrine system either directly or indirectly in the establishment of an experimental hypertension was first appreciated when it was demonstrated that the complete syndrome did not occur in the adrenalectomized animal (126, 129) even though these animals give a normal pressor response to the injection of

<sup>4</sup> More general metabolic studies relate to the influence of the endocrines (201, 202, 203, 204), age (201), and hibernation (205) on oxygen uptake by renal tissue and the distribution of various enzyme systems within the kidney (206).



renin (166). Various sterol derivatives can in themselves produce a transient hypertension in rats (167) if given in excessive doses, although one at least (testosterone) does not appear to affect the blood pressure of renal ischemic hypertensive dogs (168). The ability of antipressor renal extracts to diminish the hypertension caused by such injections has been used as an indication of its renal origin (167), but no direct evidence of renal damage was demonstrated. The effect of a pregnancy on the development or maintenance of an experimental hypertension is not clear, but it would seem in general that this condition has an ameliorating influence (169, 170, 171, 172, 173). It does not seem that this effect is due to the presence of fetal kidneys since it is observed in experimentally produced deciduomas (173).

While the general energetics of the ischemic kidney manifest no obvious derangement (174), this may not be true for some of the details of intermediary metabolism. The examination of the fate of dihydroxyphenylalanine when presented to renal tissue is particularly interesting. Dependent upon the oxygen tension, this substance may be deaminized (high oxygen tension) with the formation of a depressor substance or decarboxylated (low oxygen tension) with the formation of a strongly pressor substance, presumably hydroxytyramine. These reactions proceed in kidney extracts (175, 176), in the perfused cat kidney (175), or in the ischemic kidney into which the amino acid has been injected (177), but have not been demonstrated in perfusions of other organs. It is not suggested that dihydroxyphenylalanine or its derivative, hydroxytyramine, is itself concerned in the production of experimental hypertension.

*Renal effects of pressor and antipressor agents.*—These effects have been examined in the frog, the dog, and man. The observations in the frog cannot be applied to the situation in the mammal since the physiological control of the glomerular apparatus in the amphibian is so different from that in the mammal. It is interesting to note, however, that the engorgement of the glomeruli which follows the subcutaneous administration of angiotonin to the frog is due at least in part to an action on the efferent arteriole (178). In dogs (179, 180) and in humans (181) angiotonin or its precursor, renin, produces a reduction in renal blood flow which is out of proportion to the reduction in glomerular filtration rate. This finding is consistent with the belief that a constriction of the efferent arteriole occurs as a result of this substance. When angiotonin in-



hibitor (renal antipressor substance) is administered to normal and hypertensive dogs and to hypertensive humans, an increase in renal blood flow and a fall in the filtration fraction is usual (182). This action also involves a change in the tonus of the efferent arterioles although some afferent participation in the response can not be excluded. A fall in the renal blood flow with the development of renal incompetence may ultimately occur in the experimental preparations if the reduction in blood pressure is to a low level. The latter effect may be attributed to the mechanical interference to the renal circulation and has not been observed in hypertensive humans.

*Human hypertension.*—Certain portions of this subject are of immediate concern to this review. These relate to the applicability of the concepts derived from studies of experimental hypertension of renal origin to the analysis of human hypertension. It is established that the circulatory status of the patient with essential hypertension resembles in its essentials the hypertension produced in experimental animals by mechanical interference with the renal blood supply (115, 183). Additional evidence confirms the belief that in the human type there is usually a reduction in renal blood flow although this is not invariable. Furthermore, the relationships between renal blood flow, glomerular filtration rate, and renal tubular mass are consonant with the view that the outstanding functional disturbance early in the disease is an increase in the glomerular pressure, and that apart from other factors which may be concerned, a hypertonus of the efferent arterioles exists (51, 184, 185). This hypertonus is similar to that in other vascular areas in that it can be abolished by agents known to produce hyperemia in the normal kidney (51) and has, at least as a contributing factor, an excess of humoral pressor agents in the systemic circulation (146, 148). It is not definitely established that these agents are the same as those which result from an impairment in the renal circulation of the experimental animal, although this seems likely (183). In line with this view are the demonstrations that the disturbance in glomerular dynamics characteristic of essential hypertension is essentially the same as that which results from the injection of renin or angiotonin into normal dogs or normal man (51, 179, 180, 181) and that the same inhibitor agents (cf. 182) are effective in both types (129, 151, 157, 158, 160, 161, 164, 165).

These findings do not permit a decision on whether the renal ischemia of essential hypertension is entirely the result of circulat-



ing pressor substances (51, 184, 185) or whether it is the initial factor which causes their liberation (115, 183). It should perhaps be emphasized that the evidence is quite compatible with the view that the renal ischemia is a secondary rather than the primary event (51, 184, 185). Furthermore, a systemic agent would be the likely cause for the progressive and parallel reduction in renal blood flow and renal tissue which is characteristic of the disease in man (51). Otherwise, it is to be expected that one kidney would commonly be affected more extensively than the other, and this does not seem to be the usual sequence of events. A series of cases of essential hypertension chosen at random and studied by the unilateral technique demonstrates this point nicely (184). These studies do not deny that in specific instances unilateral disease and perhaps unilateral or bilateral renal ischemia can produce a hypertensive syndrome in man. The evidence for this is quite convincing (186, 187, 188, 189, 190, 191, 192, 193, 194).

It seems wise to suspend judgement on the relationship between renal ischemia and essential hypertension in man and to view the information obtained from experimental preparations as indicating potential rather than causal relations. It seems certain that the general metabolic and endocrine background upon which changes in blood pressure are impressed must receive further consideration. If a derangement in renal blood flow is capable of producing an excess of a pressor substance or a diminished output of an essential depressor substance, it seems equally likely that a change in the substrate presented to normal cells, the result of pathology elsewhere, or a change in the functional organization in the cells themselves, might also produce the same net result.

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DEPARTMENT OF MEDICINE  
NEW YORK UNIVERSITY COLLEGE OF MEDICINE  
AND THE RESEARCH SERVICE  
THIRD (N. Y. U.) MEDICAL DIVISION  
WELFARE HOSPITAL, NEW YORK, NEW YORK



## ELECTROPHYSIOLOGY

BY R. W. GERARD

*Department of Physiology  
University of Chicago  
Chicago, Illinois*

The war has signally decreased the European scientific output and has prevented many of the publications still appearing from reaching our libraries. Despite these limitations, the material deserving review is, as always, in excess of the available space, and the inevitable selection of fields of emphasis must be made. The exhaustive monograph of Schaeffer (1) surveys the electrophysiological literature through 1939 [see also (2)], and the symposium volumes on membranes (3) and muscle (4) contain much of relevance and will be referred to when possible for citation of earlier papers as well as new material.

Since last year's review (5), rapid developments have continued, especially in the following directions: the physical characterization of excitable membranes; the analysis of their local pre-conducted responses to stimuli; the analysis of their inherent rhythmicity; and the emphasis on electric fields and currents in integrating the action of independent units. Much of this has become technically possible by the growing use of single cell preparations and of microelectrodes.

### MEMBRANE PROPERTIES

Both the origin of biopotentials and the action of currents on cells have long been related to the properties of the bounding protoplasmic membranes; hence their structure and physical (and chemical) attributes are basic to any quantitative interpretation of their physiological behavior. It is encouraging to find a certain uniformity in these attributes for the membranes of widely different cells. Thus, per square centimeter of membrane of vertebrate and invertebrate eggs, the giant invertebrate axon, vertebrate muscle, erythrocytes, and multinucleate algae, capacitance is about  $1\mu\text{F}$  and resistance (so far as measured) some hundreds of ohms (3a, 6, 7). The membrane of *Halicystis* may be an exception (8). Even the inductive element seems to center about 0.2 H in the various nerve membranes studied (7, 9). Further, while the ohmic



resistance may be reduced a hundredfold by such physiologically dramatic changes as excitation, narcosis, or death [or denervation of smooth muscle (10)], the capacitative and inductive reactances are but little altered (3a, 7). However, fertilization alters sea urchin egg capacitance (3a), and current may alter that of liver (11).

Such evidence indicates the existence of stable structures responsible for capacitative and inductive reactance and occupying much of the membrane volume, and of separate labile elements completing the membrane and responsible for D.C. resistance. Hints as to their nature come from optical studies of films and membranes (3b, 3c). Thus, in red cell and in nerve sheaths, there is a repetition of concentric bimolecular lipoid and monomolecular protein layers; the molecular spacings are stable to heat, ions, and detergents. On the other hand, with brain lipids alone the bimolecular leaflets may be widely separated by water but can be collapsed on one another by ions, especially calcium. Likewise, the stability and thickness of the entire red cell membrane varies with the electrolyte environment. It is still premature, however, to interpret the properties of microscopic membranes in terms of their constituent molecules, rapidly though this gap is being bridged; but in the other direction, membrane properties are already accounting for many physiological phenomena.

Evidence has long existed that transverse membrane conductance is not symmetrical for the two directions of current flow [skin and other tissues (1, 12, 13)]. This rectifying action has now been shown (9) for the squid axon membrane (by means of capillary electrodes inside and outside the fiber) to be some 100 to 1—of the order of a good metal rectifier—the resting membrane resistance being reduced to one thirteenth when sufficient current flows from inside out, at the cathode, and increased eight times with opposite flow at the anode. Surprisingly, the results of stimulating single muscle fibers with electrode areas of varying length suggest an increased membrane resistance at the cathode and a decrease at the anode (4c). The asymmetry may be an expression of the different ion populations in cell protoplasm and in extracellular fluid and of the attendant concentration gradient, perhaps of potassium, through the membrane thickness. Thus, an outflowing current would sweep more potassium into the membrane from the potassium-rich interior and so increase its conductivity, while an inflowing one would carry potassium away faster than it enters from



the potassium-poor exterior (1, 7, 13). Such interpretation is weakened by the growing evidence (3a, 4m, 14) that nerve and muscle membranes, at least, are not differentially "impermeable" to sodium, as long believed, but that this ion can penetrate as readily and as rapidly as potassium. But however produced—and ion action is surely involved in the process (e.g. 15)—the nonlinear change of membrane resistance with current or voltage across it has important consequences. For example, at the anode resistance increases and the current enters a nerve fiber through a widening membrane area, while at the cathode the lowered resistance concentrates the current flow under the electrode. This accounts for the greater spread of anelectrotonus than of catelectrotonus. [See, however, the report that these are symmetrical in fresh nerve but greatly altered by carbon dioxide (16).] Rectification may also explain the delayed excitation by alternating currents (7).

Impedance, measured across the whole fiber (17), decreases at a cathode and, with currents over half (or less) rheobasic, shows oscillations, from the first of which a propagated impulse takes off on threshold stimulation. The membrane potential behaves similarly (9). Since present evidence indicates no critical change in membrane impedance on passing from local to propagated effects, and since no conductance change appears when an impulse reaches a resting region until the action potential rise passes its inflection (indicating current in the capacitative element only) and the change is then an increase (indicating outward current flow through the rectifier element while current flows inward through the whole membrane), the conductance change may be especially concerned with membrane repolarization and recovery (7, 17). At least conductance is a more sensitive index to physiological state than is action potential (9). Resistance decreases and rectification is lost as a fiber dies, and a largely reversible decrease is produced by cocaine or veratrine (18). The rhythmic impedance changes with a five-minute period, observed in trout eggs and abolished by narcosis (19), deserve mention in this connection.

Another important finding is the fairly regular presence of an inductance in this axon membrane (20), manifest directly with test current frequencies below 150 to 300 cycles. The nature of the inductive element is unknown, but Cole (7) points out the similar decrease of resistance with increase of current shown by a carbon filament or by a piezocrystal and considers the possibility that the



fiber membrane, at least semicrystalline, may have piezoelectric properties.<sup>1</sup> This would account for the properties of mechanical stimulation but should also require a birefringence change—still undetected—during conduction. From the given membrane resistance and capacity, the time constant for discharge (and so for excitation) would be 0.4 msec.; and the added inductance would permit spontaneous oscillation at some 300 per sec. This time constant and oscillation period are essentially the ones observed for this and related nerves, even for veratrinized cat nerves (21). [If all membranes were as physically similar as indicated earlier, these characteristics would be alike in all tissues. Since they are not (4c), even for cell body and axon (22), either the membranes differ greatly or still other factors are involved.] Further, the time constant increases at the anode, as it should; and indeed the two factor excitation theories reduce to equations in resistance, capacitance, and inductance (7).

The potential across the axon membrane, at rest after impaling on a capillary electrode, averages 51 mv. (23), and a similar value, 54 mv., has been obtained from impaled sartorius muscle fibers (24). In both cases, as in impaled *Halicystis* (3e), the potential falls with increased external potassium concentration and, in the nerve, has even been reversed by 15 mv. (the outside becoming negative). Action potentials, although about what would be expected from the potassium ratio inside and outside the fiber, are regularly less but sometimes definitely more than could be accounted for by a concentration potential (25). A nerve action spike does not merely reduce the resting potential to zero but momentarily reverses it by over 50 mv.—an observation (23) irreconcilable with the simple depolarization model, except as it may result from the membrane inductance. The inductance may likewise contribute to the positive afterswing, some 10 mv., which follows the "monophasic" membrane spike (26).

Physically determined relations obviously exist between the membrane impedance and the "passive" potential change induced

<sup>1</sup> Dr. A. Weinberg, to whom I am indebted for much profitable discussion of this section, has called my attention to the suggestion by L. Hermann in 1899 [*Arch. ges. Physiol. (Pflügers)*, 75: 574-90] of an inductive element in nerve and that by W. Sutherland in 1905 (*Am. J. Physiol.*, 14, 112-19) of a piezoelectric structure in its membrane. Neither seems to have been taken seriously by physiologists.



by external currents. A decrease in the normal potential across the membrane decreases the resistance, and a decrease in resistance decreases the IR drop. As the membrane moves towards or into the excited state, both effects occur. Cole (7) has again suggested that excitatory state may be identified with an active change of membrane potential; Katz (27) suggests that a change in resistance is the critical factor, the potential following passively. If the last impulse a squid nerve can conduct shows an action potential but no impedance change (Cole, personal communication), the former view gains support. Also, frog nerve actively controls its membrane potential against change by polarizing currents (16). It is too early to decide these matters but important to recognize that proof of the nonlinearity of behavior of the membrane system may offer a physical basis for the phenomenological description of nerve and other tissues as relaxation oscillators (28, 29, 30, 31) with their self-sustaining responses.

#### THE RESTING POTENTIAL

The discussion so far has been based mainly on the results of subjecting a given membrane region to applied currents, of supplying the driving battery. But cells contain their own batteries and maintain a potential between interior and exterior. This has regularly been located, in our thinking, across the intact membrane, and indeed the direct measurements on impaled cells show it to be there. However, conflicting evidence exists. The potential fields in and about sartorius muscles with varying injuries and placed in varying conducting systems can be matched by a dipole model corresponding to the injured end (negative outside), but not one corresponding to the cylindrical intact surface (positive outside), this fact suggesting that the injury potential arises as a dipole at the injured end (32). But Blair *et al.* (33) insist that, if the usual membrane hypothesis is valid, "the dipole theory is a direct deduction from electrical potential theory . . . based on experiments much more conclusive than living tissue is likely to provide." Perhaps the model experiments differ from the tissue ones in conditions of boundary resistance and current flow. Direct exploration with a microelectrode, inside and outside a muscle fiber, shows the potential across the membrane to decrease roughly exponentially from full size at 2 to 3 mm. from a cut to zero at the cut end (24).

Other work (34) shows that the sartorius injury potential is



modified by external sodium or potassium applied to either cut or intact surfaces, the injured surface being only less sensitive to sodium. Since in these experiments the muscle stood some time after injury, a certain amount of membrane repair must have taken place. Also, the voltage measured between two points on a tissue depends not only on the E.M.F. generated but on IR losses in the entire circuit, so that resistance changes away from the battery would influence the readings. On the other hand, it is perhaps time to seek systems in addition to membranes which can develop potentials in living matter. Membrane potentials regularly show a deficit from the theory for concentration difference, perhaps because of opposing potentials (25, 35, 36), and much evidence (see pp. 338 and 347) shows considerable voltage gradients along cells and in tissues where no complete transverse membrane is present to account for them. Whether oriented molecules or micelles acting as diipoles could serve as a machine to maintain voltage and current with the aid of metabolic energy remains to be explored. At least muscle birefringence changes must be accompanied by impedance changes (4h) and are, in turn, related to metabolic events (37). Blinks & Pickett (38) could not alter the potential of *Nitella* with externally applied oxidation-reduction systems [but positive results are reported for frog skin with hydrogen peroxide (39)]. Blinks & Pickett quote Umrath's observation that two microelectrodes within the cell failed to register a potential change when an activation wave passed—which speaks against the above possibility.

Certainly a membrane, even when entirely passive, affords a mechanism for converting chemical into electrical energy. Diffusion and concentration potentials across cell membranes are largely determined by the concentration and mobility of various organic and inorganic ions within the membrane. By appropriate treatment of the inner or outer protoplasmic surfaces of the several large algal cells, the resting, concentration, and action potentials can be varied in parallel with the sensitivity to ions, especially potassium (3e, 3f). Thus, when differential permeability to sodium and potassium is lost due to raised or lowered conductance—e.g., by oxygen lack or narcosis, which increase the membrane resistance of *Halicystis* (40) but lower it in nerve [compare with model experiments (41)]—so is the concentration potential. Also, the monophasic action potential of *Chara* can be changed into the diphasic one of *Nitella*, and vice versa, by treatment which, respec-



tively, renders the outer surface sensitive to potassium (as the inner one is regularly) or insensitive to it (42). Again, the presence of organic molecules and ions markedly alter resting potentials and the effects of sodium and potassium on them, presumably by altering ion mobilities (43).

The influence of the common cations on physiological state is usually attributed to their action on membrane potential, permeability, etc. Recent work on the changes produced by potassium and calcium on discharge of receptors [e.g. of cats' vibrissae (44)], frog muscle irritability to currents (45), crustacean muscle response to nerve stimulation (46), vasomotor muscle contraction in response to nerve impulses or epinephrine (47), and invertebrate ganglion spontaneous discharges (48, 49, 50, 51), confirms the general relation. Striking differences occur, however, in the potassium action on similar cells in different species (increased number of nerve cells discharging in some and increased frequency of discharge by each cell in others, these effects being antagonized by calcium in some cases but not others) or even in the same animal (depression of claw response to the slow motor fiber, increase in response of the same muscle fiber to the fast motor fiber).

To the extent that membrane potentials depend on maintained asymmetries of inorganic ion concentrations, despite their movements across a membrane, metabolic ions or complexes must continually be available for exchange. Various agents influence membrane potentials by their control of cell metabolism, especially of acidic ion production (3); and the high concentration of dicarboxylic amino acid anions in invertebrate nerve protoplasm (52, 53) is obviously important in this connection. The ability of oxidized collodion membranes, with their fixed acid groups, to give nearly theoretical concentration potentials (54) is also noteworthy in view of the presence of acid lipids in membranes. The special relation of acetylcholine to model (55) and membrane (56, 57) potentials is also worthy of note.

But if a membrane potential must be actively generated in any event, then a pumping action might work even without, certainly in addition to, these differential mobility mechanisms. This has been urged (3d, 4m, 34, 58) on the basis of experiments [see also (14)] showing the free diffusability of sodium and chloride, as well as potassium (59), across nerve and muscle membranes and demonstrating the loss of the ability of a muscle to keep potassium



concentrated when its energy supplies from respiration and glycolysis are simultaneously blocked (60). Sodium, consequently, is pumped out by the membrane to maintain the low internal concentration, or potassium is pumped in—more likely the former (4m); in addition, potassium lowers potentials more than it should thermodynamically (e.g. 36) by its ability to increase the concentration of ions in the membrane (by increase of "pore size" and conductance).

The specific conductance indicates that ion concentration times mobility in a membrane is some  $10^{-9}$  that in protoplasm, but that for a given potential across the membrane one thousand ions pass through for each nonpenetrating charged pair forced against opposite sides (3a). Putting the situation backward, with potassium and univalent anions as the moving ions, the measured membrane resistance and voltage would cause a flow across the membrane of  $10^{-10}$  moles of potassium per cm. sec. Potassium can re-enter a depleted muscle at better than one thousand times this rate (3d). The nature of the membrane pump or battery remains unknown, although its dependence on metabolic energy is well established. The report (61) that the resting potential of nerve is destroyed by supersonic waves only when oxygen is present during or following the radiation is perhaps relevant here. Potential changes in the cortex of the cat are found to fail in parallel with oxygen lack but not with loss of phosphorylating systems (62).

#### THE RESPONSE

When the resting membrane equilibrium is sufficiently disturbed, the system discharges intrinsic energy, and a self-maintained response is transmitted. With less displacement, a local response may occur which subsides in damped (exponential) fashion (e.g. 63), with decrementing oscillations, or even with incrementing oscillations and ultimate discharge (e.g. 64, 65). A sharp distinction has regularly been made (e.g. 1) between the purely physical electrotonic potential, generated by the applied current in a cable-like conducting system, and the physiological subpropagating potential superimposed upon this at the cathode when currents exceed a fraction of the rheobasic strength. It is doubtful, however, that this sharp line is valid, any more than is that between local and all-or-none responses; there is probably a continuum of change in the membrane conductance as current in it shifts with



the duration of applied voltage (5, 66). And membrane conductance (and rectification) is emphatically related to physiological state.

Yohimbine does not affect the refractory period of the local response (cf. 63) of lobster axons (67) but increases that of the action potential to over a second; and with the aid of this, and of other agents which stop propagation entirely, the local potential can be studied in detail. Added potassium first exaggerates but in higher concentration abolishes it; calcium diminishes it (67). We have long had evidence (e.g. 68), never entirely satisfactory technically, that oxygen consumption is maintained at a higher level in a region of nerve kept cathodal—a further instance of the close relation of membrane and physiological states—and Bronk *et al.* (68a) have shown that there is no break in the progressive increase of resting respiration, known to accompany calcium diminution, when conducted impulses appear in increasing numbers.

The gradation, then, from the passive electrotonus to the active propagated response is continuous; current through and resistance of the membrane conductance are related to each other and to metabolism; changes in these are the physiological response, which dies locally or grows to all-or-none magnitude depending on the quantitative relations between activated and inactivated regions (length constant, excited area, safety factor or ratio, etc.); and the action potentials and currents, which are the immediate agent for spreading excitation from point to point, are actively generated in the responding membrane. The fact that the action spike is not entirely a simple depolarization of the responding region but is an active change of its local battery is at last established by evidence already cited, such as the independence of resting and action membrane potentials, as well as by mathematical consideration of the shape of the potential and impedance changes (16, 69).

Given, then, potential changes at an active membrane region, current must flow through neighboring conductors as determined by physical quantities, mainly the resistances of axoplasm, membrane, and outer medium. The relation of fiber diameter and resistance to conduction velocity has been summarized, mainly for vertebrate fibers (70), and new data are available on large invertebrate (71) and vertebrate fibers (72). The influence of external volume on velocity has been analyzed mathematically in terms of



actual current distribution (73), and the ability of an asymmetric outer conductance to alter the magnitude and form of the action potential has been measured and interpreted for the crayfish axon (74) and has been invoked to explain some positive potentials in brain stem nuclei (75). Records from a single medullated fiber in oil (76) directly demonstrate the greater action potential obtainable at a low resistance node than over a myelin segment, and that the latter derives from spread from adjacent nodes. Block of an impulse at a node occurs in all-or-none fashion (gradation in local response might have been missed) and the impulse, when blocked, still produces an electrotonic potential, of one fourth spike height at the node beyond. The published curves contain evidence that the active potential response starts well before the inflection on the rising potential limb (see p. 331).

Variable potentials exist in tissues other than those directed transversely across cell membranes or longitudinally between active and resting regions. Indeed, over the microscopic dimensions of a neuron cell body, propagating activity could hardly account for the prolonged rhythmic potential waves—from tens to thousands of milliseconds in duration—nor would a uniformly distributed change in membrane potential be detectable by external electrodes. A maintained potential along the dendritic-axonic axis of the cell, able to vary “spontaneously” and to be discharged or enhanced by appropriate external influences, seems to be required. Such a “somatic” potential, although long in evidence, is only recently receiving proper attention (e.g. 77). Subordination effects on peripheral nerve (78), on sympathetic trunks (79), and in the spinal cord (80) have been related to such potentials and the associated electrotonus produced by resulting currents; correlations of such axial potentials with neuron threshold and discharge have been pointed out (77, 81 to 85); and direct evidence has been offered, by polarizing neural masses, that the anticipated changes in activity accompany the experimental changes in tissue potentials (85, 86). [Compare with those in the heart (87).]

Further, it is well established that considerable potential differences exist along the surface of uninjured tissues, especially the nervous system (80, 85, 88, 89), even when they lack parallel longitudinal elements. [A similar anterior-posterior potential gradient exists in salamander embryos (90).] Other cases, relating potentials of large body regions to tumors (91), ovulation (92), or sleep and



anesthesia (93), are less convincing, if only because the notoriously variable skin potential is in the circuit. But the skin potential itself is the expression of electrical asymmetries along the axes of epithelial and gland cells (94), as are the similar potentials across mucous membranes and glands (95), smooth muscle (4e), the eyeball (96), single eggs (97), plant nodes (98), etc., also expressions of cell polarity.

#### INTERCELLULAR CURRENTS

Since temporary or maintained potentials are present, currents must flow through surrounding conductors and, in the case of neighboring physiologically responsive structures (besides inert tissue fluid), should change their state. This is now conclusively demonstrated, not only in the favorable case of nonmedullated large axons placed in apposition, for which Arvanitaki (99) suggests the name "ephapse" to replace "artificial synapse," but also for the following: medullated nerves near an injured region (catelectrotonus) (100), on direct polarization (101), or after administration of veratrine (102); the spinal cord when injured (103) or strychninized (104), and the brain under caffeine (84, 85); and nerves within the mass of a muscle suddenly active (105). [See also studies on prostigmine (106) and on veratrine (107) discharges from the end plate, and on muscle impulses discharging nerves in physostigminized preparations (4n).] In each case, the brief currents associated with activity of some nerve fibers, nerve cells, or muscle fibers suffice to excite (or condition) nearby nerve fibers or cells. The cross-stimulation time for nerve may be as long as 30 msec. in veratrine (102), suggesting local potential oscillations (64), but is more commonly about 2 (101), or even 0.2 msec. (103), suggesting a direct electrical stimulation. [Compare this with synaptic delays in crayfish ganglia of 2 to 30 msec. (50).] Since active fibers would be better conductors than inactive ones and so shunt intercellular currents, Blair & Erlanger (100) suggest that shunting may make the late impulses which reach a synaptic region less effective than the first one. [Compare this with the greater spread of cord potentials into a stimulated than a resting root (108).] Similarly, the number and disposition of glial elements about conducting and junctional structures may have an important influence on current flow and physiological behavior.

Aside from the contribution such currents must make to junc-



tional transmission (special cases given later), they seem to play a dominant role in the synchronization of rhythmic neurons and in the spread of certain types of waves through neural masses. [See, however, studies on cortical synchronization by a special fiber system (109), on the block of epileptic spread by cuts in the brain (110), and on evidence from insulin and strychnine action of the existence of special rhythmic cell groups (111).] Thus, very regular large potential rhythms remain in the isolated frog brain after synaptic conduction has been blocked by nicotine, and the characteristic potential wave induced by caffeine continues its normal slow travel from olfactory bulb to occipital pole even across a clean anatomical section of the entire brain (77, 84, 85, 112). Similarly, the large potential waves evoked by strychnine in the spinal cord of the cat are synchronous at all levels, even after transection; they are modified along the whole cord by a single afferent volley more promptly than conducted impulses could travel the required distance; and they can be altered independently of reflex conductivity (104, 113). The sequence of muscle responses in man has also been interpreted (114) in terms of a concentrically spreading central excitatory state. Neural interaction and integration by such nontransmitted potential fields and currents help account, in fact, for many phenomena of a more general character—mass action, equivalence of stimuli, total behavior patterns, conditioning, etc.—which resist explanations limited to the travel of nerve impulses in anatomically determined pathways, including those with recurrent circuits (77, 85).

Even in the finer balance of neuron action, which is predominantly under the control of impulses traveling respectably along nerve fibers, field currents may be important. The correlation of after-potentials with excitability, established by Gasser (115), is receiving continued confirmation (116, 117, 118) for cell bodies as well as axons. Evidence is also growing that cell discharges are related to cell potentials (81, 85, 104, 119, 120, 121, 122, 122a). It is usually assumed that such after-potentials represent alterations in the transverse membrane potential, but it is possible, or probable in the case of cell bodies, that they represent also or entirely alterations in the longitudinal somatic potential. And such over-all cell potentials must produce currents which cross the irritable membrane of the cell and so algebraically sum with externally



applied stimulating currents or with locally applied action currents of impinging impulses to alter cell behavior.

The problem has long existed of how excitatory impulses arriving on widely separated dendrites of a single neuron could pool their influences at the axon hillock and, more difficult, of how excitatory and inhibitory ones could do the same. The explanation of central inhibition in terms of competition for interneurons, while supported by further evidence of precise impulse timing (123), has been criticized on other grounds (77, 124, 125). Our increased knowledge of the magnitude of spatial spread of electrotonic and local-response potentials has made a rational interpretation of such spatial summation more satisfactory (126), but still an integrating mechanism for the whole cell is needed. An early suggestion (68, p. 547) has recently been expanded (77, 82, 127, 128) to account for this. If excitatory and inhibitory endings were asymmetrically distributed with respect to the axis of a neuron, the same junctional change would produce in each case an opposite effect on the somatic potential. Thus, impulses arriving on the dendrites would make them more negative and, if these were originally negative to the axonic pole, would increase the somatic potential gradient, while impulses arriving near the axonic pole would flatten the gradient. Opposite changes in current and physiological activity would result in each instance. In at least one case, the Mauthner cell, such a polar distribution of different synaptic endings has been established.

The early inhibition of motor cells produced by antidromic impulses in adjacent ones, presumably via axon collaterals though possibly by intercellular currents (129), may have a similar explanation. [See also the direct motor cell inhibition produced by dromic impulses (130).] The striking increase in reflex (131) or spontaneous (132) discharge of the cord produced by cooling, the convulsive discharges and potentials obtained at the periphery of a frozen cortical region (133), and the multiple muscle responses to a single nerve impulse in cold but not warm physostigminized nerve-muscle preparations (134) may be related to a prolongation at low temperature of potential changes and of other cell properties, e.g., excitation constant (4c), which favor the action of such intercellular or synaptic potentials.



## JUNCTIONAL TRANSMISSION

Some reference to the mechanisms of transmission between cell units—receptor-neuron, neuron-neuron, neuron-effector—is inevitable in any consideration of bioelectric phenomena. The problem can be exemplified in the case of nerve-muscle, not treated elsewhere in this volume. That acetylcholine, potassium, and other chemical agents profoundly affect the activity of many cells is unequivocally established; that one of these is the transmitter in any particular case is less certain. The following facts all indicate that these agents are involved in roles other than that of simple junctional transmitter: cholinesterase is present in and acetylcholine is liberated from simple conducting nerve trunks (57, 135, 136); the acetylcholine content of sensory nerves is markedly different from that of motor or autonomic nerves (137); acetylcholine decreases sharply in degenerating sectioned nerve (137), as does acetylcholine in brain (138) and esterase in nerve (139) in the degeneration accompanying vitamin B<sub>1</sub> lack; the high esterase content of the electric organ parallels the performance of the effector rather than the profusion of the junctions (56); some invertebrate junctions seem insensitive to the acetylcholine group of activators and esterase inhibitors even though the tissue esterase content is high (50, cf. 140); epinephrine directly influences nerve action potentials (141); nerve-free smooth muscle in the chick amnion responds to these drugs in the same minute amounts and in the same manner as does neurotized muscle with the usual neuromyal junctions (142); physostigmine increases the size of isolated muscle fiber contraction (143); the partial curarization defect in myasthenia gravis victims exists with no defect in acetylcholine liberation (4k); barium, with no antiesterase activity, can duplicate the action of physostigmine in making single nerve impulses give muscle tetani (4f); and curare can antagonize physostigmine without decreasing its antiesterase action (4n); etc. On the other hand, the confirmed high concentration of esterase at skeletal nerve-muscle junctions (144); the familiar functional changes produced by acetylcholine, physostigmine, and other agents (e.g., 4e, 4f, 4k, 134, 145, 146, 147); etc.—all these indicate that chemical agents do contribute to transmission.

The view seems to be gaining ground that the acetylcholine group of agents, as well as potassium (148), serves to modify the responsiveness to the transmitting agent of the to-be-activated



unit, rather than that it is the transmitter itself (4f, 149, 150). The somewhat neglected evidence of Cowan (151), showing a strong influence on muscle membrane potentials of acetylcholine, is re-emphasized by the finding (150) that the usual close arterial injection of acetylcholine renders skeletal muscle more irritable to electric stimuli. Curare, which renders muscle nonresponsive to acetylcholine (4k, 147, 151), prevents the acetylcholine potential change (151) and reduces the end-plate potential (4n).

The end-plate potential behaves in considerable detail as if it were the final link in starting a conducted response in the muscle fiber. In the frog successive nerve impulses facilitate easily, and each successive end-plate potential is augmented (4f, 4n, 152), whereas in the cat neither is the case. Physostigmine increases and prolongs the end-plate potential, and curare decreases or abolishes it. Guanidine, which decurarizes for single nerve impulses yet exaggerates the Wedenski inhibition of a series, increases the end-plate potential of the one impulse but hinders its repetitive cumulation (4f, 153). Small end-plate potentials sum with the passing action potential in a muscle fiber to speed conduction past the end plate (4n), while larger ones depolarize and can block conduction at the junctional region (4f). The decurarizing action of a local cathodal current in the end-plate region (154) may be recalled. The end-plate potential also prolongs the refractory period of muscle by one fourth, and physostigmine makes both endure longer (4n, 155).

It must be pointed out that, in crustacean muscle, contraction or its inhibition can occur independently of action potential changes (not measured locally—see p. 346), and even in striated muscle the size of the potential spike [and the first negative after-potential at least, though perhaps not the positive one (156)] can vary independently of the magnitude of the contraction (4g), as is the case under the action of veratrine or yohimbine (156). [See also studies on complex spike potentials (157, 158)]. But this is only additional evidence of the separability of conduction and contraction mechanisms in muscle. Successful measurements on a single nerve-muscle junction (159) leave little doubt that the end-plate potential is the effective stimulus for initiating the propagated muscle fiber response, for the latter starts at whatever time the former, altering under curare action, reaches a given absolute value, one third its normal size.



Since a constant current less than 1 per cent above rheobase can cause repetitive responses of a single muscle fiber (4a), since the end-plate potential is a muscle membrane depolarization which spreads electrotonically (152), and since the action currents of nerve terminals must pass across adjacent muscle, it is possible for junctional transmission to be entirely electrical. However, it remains probable that acetylcholine contributes importantly to the production of the end-plate potential—much of the above evidence would fit this—just as it may contribute to the nerve or muscle action spike.

#### SPECIAL TISSUE POTENTIALS

*Heart.*—Potentials in this syncytial mass of muscle are being analyzed into their elementary form and related to the mechanical response. Effective monopolar leads are obtained by local injury [pressure (160); suction (161)] or potassium (162) at one lead, the other then recording a monophasic potential under proper conditions. Since, under ordinary conditions of EKG recording, the monophasic response of the right ventricle is upright and that of the left is inverted and slightly later in the cycle, their algebraic sum accounts for the QRS complex (162). The potential level during the S-T interval and the size and direction of the T wave similarly depend on the time course of the right and left cardiograms and can be controlled by altering the temperature of either ventricle (163). The R complex can be similarly modified and, in general, the EKG from various leads and conditions is interpreted in terms of opposing right and left potentials (164). Other work (165) indicates the importance of like differences between base and apex and emphasizes the role of ions; and still other studies (160) further analyze the recorded potentials in terms of rings of partial or complete depolarization (systole) and repolarization (diastole) spreading from an active region.

The simpler case of an isolated strip of turtle heart, usually driven from one end, has been studied (33) for potential and mechanical changes. The Q wave (diphasic) is equated with the arrival at the recording electrode of the longitudinally spreading depolarization dipole, and the reversed T wave with the similar arrival of repolarization. The cells may remain depolarized for two seconds or more, on this interpretation, and are refractory while in that state. Further, the mechanical response is initiated by de-



polarization and cut off by repolarization, whenever this latter is caused to occur. It is also reported that the wave of repolarization may travel more slowly than the wave of depolarization (33). (A similar phenomenon in nerve or muscle would manifest itself in changed time relations with distance traveled of the rising and falling limbs of the spike; this has not been noted—but hardly looked for—in single axon records.)

Studies on turtle and dog hearts (161, 166, 167, 168) agree with those on heart strips in relating the start of contraction to the electrical events—maximal current flow—as the depolarization wave arrives. The “vulnerable period,” at the end of systole, when applied currents can start ventricular fibrillation (169), may be an expression of membrane instability during early repolarization and so comparable to the repetitive discharges obtainable from nerve and skeletal muscle. Indeed, cathodal polarization of the ventricle causes a potential rhythm, irregularly centered about a 40 msec. period, from the oscillations of which beats may arise (170)—a finding strongly suggestive of the similar phenomena already considered in giant axons.

*Smooth muscle.*—There is increasing recognition of several types of smooth muscle which may differ more from each other than some do from striated muscle. Rosenblueth (4e) would distinguish between long- and short-fibered muscles; Bozler (4d), between multifibered and syncytial ones, but in neither case are the categories too satisfactory. The former emphasizes the low or absent electrical excitability of the denervated nictitating membrane and anestrus uterus, as compared to their responsiveness to epinephrine and nerve impulses; he considers their complex potentials as a nonpropagating—since varying electrode position does not alter latency and diaphasic interval [but see (171)]—asymmetric depolarization of each muscle cell at a similarly oriented end; and insists on their graded response and absent refractory period. He concludes, for these cases, that the muscle cells have no conducting mechanism and are excited exclusively by neurohumors. However, potassium and calcium alter vasoconstrictor responses to epinephrine and to nerve impulses independently (47).

Bozler, however, finds propagated all-or-none impulses in the uterus, gut, and ureter. Even when excitatory nerves are not present, electric stimuli give responses attended by traveling action potentials which are monophasic or diphasic in the usual relation



to a crushing injury. Further, spontaneous or stimulated mechanical responses are regularly associated with repeated or fused potentials, which vary in number and frequency (and size) with the magnitude of the contraction. He interprets local responses in the uterus as due to block in the conducting muscular syncytium because of high threshold (172); and the variable threshold of smooth muscle is considered as a major difference from skeletal fibers. In the nonpregnant uterus, for example, nerve or epinephrine action causes a local stimulation but blocks conduction by lowering irritability (173); theelin treatment leads in a few days to a threefold increase in the resting potential of the muscle cells and a fivefold increase in their electrical excitability—and excitation is propagated (174). Correspondingly, as pregnancy advances, spontaneous or epinephrine-evoked contractions are associated with diphasic propagated spike potentials repeated regularly about 3 per sec. (175). Potential and mechanical responses are also closely related in vaginal contractions (176). Recalling the decreased electric and increased drug sensitivity of degenerating skeletal muscle, the ease of obtaining localized contractions (4b), and the absence of a refractory period and all-or-none response (177), it is perhaps premature to exclude a membrane conducting mechanism in the case of smooth muscle.

*Invertebrate muscle.*—Invertebrate smooth muscle exhibits a similar marked difference in individual cases, extending here to variation in the number and kind of excitor, inhibitor, and other types of nerve fibers reaching each muscle fiber (4j, 178). In crustaceans, for example, one motor fiber causing a fast contraction and another causing a slow contraction (and then only with a series of impulses) end as a feltwork along the entire muscle fiber, well intermixed with like endings of one or more inhibitor fibers. Muscle action potentials are set up by excitatory nerve impulses and may show a marked facilitation on repetitive stimulation, as does the following contraction; yet the action potential and the mechanical response can vary quite independently. Thus, a single muscle may give no contraction despite a large potential on activity of the fast nerve fiber and a good contraction with a negligible potential on activity of the slow one.

Further, inhibitory impulses, which evoke no electric sign themselves, can entirely stop contraction in response to concurrent motor fiber stimulation without altering either the excitation ac-



tion potential or the excitation facilitation which accumulates and finds expression after inhibition ceases. An inhibitory impulse immediately preceding an excitatory one can, in some cases, greatly depress the potential response, but again not in parallel with the decrease of contraction (179). A similar independence of electrical and mechanical muscle responses is reported for a snail columella nerve-muscle preparation (180). Wiersma (4j) postulates, on the basis of these findings, the series: nerve impulse—transmission process—muscle potential—transmission process—contraction, with facilitation or inhibition able to act independently on either intercalated transmission mechanism. Such findings certainly reveal a wealth of possible relationships; it will be of great importance to check them, and those on other smooth muscles, with local recordings from single units (even if not isolatable) with microelectrodes.

*Receptors.*—Aside from the nerve action potentials set up by stimulation of receptors, the receptor elements themselves, e.g., the cells of the spiral organ in the ear (181), consistently manifest electrical responses. Cochlear potentials in the bat have been shown to follow supersonic air waves to 100 kc., and such high frequency reception guides the animal in flying (182). A steady potential is maintained along the eyeball axis (96), and the multiple potential waves with which the vertebrate retina responds to light are well known. Similarly, in the squid eye potentials appear across the receptor elements on illumination—a negativity of the outer surface and a positivity of the basal surface are considered, on the basis of their differential behavior under varying conditions, as two separate, opposed potentials (183). In the receptor layer of the water beetle eye, illumination evokes a smooth potential, the outer surface becoming some 10 mv. negative, which spreads electrotonically to the optic ganglion (184). This may resolve into two like-oriented potentials, one related to pigment-cell migration and the other to the discharge of nerve impulses. The parallel course of the potential and the discharge is further evidence for the general role of receptor currents in initiating the afferent impulses. Other studies on visual potential responses in grasshoppers (185, 186) and in *Mya* (187) may be noted. [See also studies on receptor fields and summation in the frog retina (188).]

*Other potentials.*—A potential, averaging 6 mv., across the intestinal mucosa is reported to decrease during secretion and in



proportion to the quantity secreted (95). Abdominovaginal potential differences, which change slowly in sleep (189) and sharply on ovulation [(190), cf. (92)] have been long recognized in mammals, and similar ovulation potentials have been reported for the hen (192). An asymmetrical meridional potential of the frog egg is related to morphogenesis, as evidenced by the appearance of the embryo's primary axis in that meridian showing the greatest potential (some 3 mv.) between animal pole and equator (97). Direct tests on chick embryos failed to show any influence of weak direct currents on the course of development (193), but there is some evidence of currents influencing hydranth regeneration (194). The existence of steady potentials in plants, 80 mv. or more between apex and base of the stem, has also been related to morphogenesis (98) and to photosynthesis (195). It is disputed (196, 197) whether electrophoretic movements of auxin is an important part of the mechanism. Action potentials obtained by stimulating apples, potatoes, etc. with induction shocks start within a fraction of a second but last for minutes (198). They arise in the outer layers which behave as an anion-impermeable membrane, constitute a depolarization of a resting potential (positive outside), and are abolished by cyanide. Further, excitation—measured in terms of the electric response—obeys the usual intensity-time law and indicates three excitable elements (as in the case of muscle) with chronaxies of about 10, 100, and 1000 msec.

*Skin.*—The potential and impedance of frog and mammalian skin has been much studied. Strong alternating currents (electroshock treatments) are again (cf. 1) shown to greatly reduce skin impedance in man (199); weak narcotics (homologous alcohols) increase and stronger ones decrease frog skin permeability (tested by impedance and by sulfocyanate ion penetration); still stronger solutions cause an irreversible increase (41, 200). The electrotonic potentials produced in the human skin exposed to currents through different external electrolytes indicate that it is selectively permeable to anions (201). The skin action potentials produced by nerve stimulation can be paralleled by external application of acetylcholine (202). The central nervous system normally controls the skin potential, via the nerves, since pithing or nerve section can halve it while strychnine injections raise it (203). The polarization potential of frog skin and its discharge on direct stimulation of the skin are altered by external hydrogen and polyvalent ions only in



a cathodal region, by hydroxyl ions in an anodal one (204). The results are interpreted in each case in terms of adsorption of oppositely charged ions on the appropriately charged surface of a polarized membrane, and are related to rectification phenomena.

Comparison of the skin oxygen consumption with the electrical work done by the skin, serving as a battery in an external circuit (205), gives a measured efficiency in producing electrical from chemical energy of over 2 per cent and an estimated corrected one of 6 per cent. Figures for respiration with no external circuit are needed to estimate the fraction of metabolic energy really concerned with current production. Another approach to the metabolic origin of the frog skin potential is the application of oxidation-reduction systems, inhibitors, and substrates (39). Hydrogen peroxide increases the skin potential, is antagonized by cyanide but not by urethane, and is further enhanced by pyruvate. The results are interpreted in terms of a oxidation-reduction potential equilibrium. The relation of skin potential to the differential outward diffusion of ions continuously produced by metabolism, e.g., bicarbonate, has been considered earlier [see also (206)].

#### APPLIED CURRENTS

The action of applied currents, partly reviewed in earlier sections, demands additional consideration. The cathode and anode of a constant current exert differential actions on membrane or tissue resistance, potential (aside from immediate polarization), irritability, and response; and similar changes are produced at the poles of an alternating current. In the latter case, rectification causes each pole to act more as a cathode than as an anode so that secondary anodes must form to both sides of each electrode. Even with constant currents, any irregularities in the conducting network might generate secondary poles. The possibilities of producing complex and variable changes, especially in a tissue as compared with a single cell, are thus great.

The work of Rosenblueth *et al.* emphasizes these complexities in the case of medullated nerve trunks of the cat. Alternating currents are found to influence resting potential, irritability, and spike potential in varying degree and direction, and to cause changes in each property largely independently of the others (21, 207). [Similar independent variations with season have been reported (208).] A direct current can increase or decrease excitability at either pole



and, indeed, may induce along the nerve a curve of threshold values which crosses normal five times. Such electrotonic effects can persist for minutes even in distant (8 cm.) extrapolar regions (209). Further, both anode and cathode can initiate nerve impulses (often repetitive) at either make or break, contrary to Pflüger's law (210). [Although a possible action of spurious poles is considered by the author, this complicating factor can hardly be dismissed on the evidence to date.] The intricate phenomena, even when a single muscle fiber is excited through microelectrodes (4b, 211), may be recalled in this connection. Also, with a microelectrode inside such a fiber and an indifferent one outside, the fiber responds to a sharp shock or a condenser discharge only when the outside electrode is cathode (24).

In the frog nerve-muscle preparation, the long-known greater stimulating efficacy of ascending currents at the muscle end of the nerve and of descending ones at the spinal end is interpreted in terms of the cathode position relative to the heavily myelinated central ends of the nerve fibers or the poorly myelinated muscle ends, the latter permitting more current dispersal (212). The known shift in the cross-sectional position of motor fibers along the nerve length should also be considered (213). An alternating electric field stimulates only that stretch of a bent nerve which lies parallel to the field (214); this is undoubtedly related to eddy currents, as in inductotherm therapy (215). Under the experimental conditions, seven times as long a stretch is required for maximal excitation when the central rather than the peripheral part of the nerve is so oriented. Varying short circuiting of eddy currents by inactive tissue and fluid is probably responsible for this difference.

Constant currents, passed through the thickness of the ventricular wall of the isolated frog heart, accelerate (outer surface anode) or slow and stop (outer surface cathode) the beat while flowing (87) and produce the reverse after effects on ceasing [(216), cf. (170)]. Invertebrate hearts are accelerated by cathodal, slowed by anodal, polarization of the sinus (217). [Compare the effects on brain rhythms of currents passed across the outer wall of the cerebral hemisphere of the frog (85), or through the cat brain (218).] Current effects sum algebraically with pressure effects, as if both act on the same mechanism (219). The duration of action of acetylcholine is prolonged at the anode and shortened at the cathode; that of epinephrine is altered in the opposite direction



(220). Polarizing the pancreas is reported to alter the volume, organic matter content, and tryptic activity of the pancreatic juice (221).

The influence of currents on the nervous system has been much studied and is receiving renewed attention because of the practical possibilities of electroshock therapy (222, 223) and electroanesthesia (224). In the former, a sufficiently intense brief alternating current passed between the temples gives an immediate tonic and clonic convulsion followed by depression (225, 226). The late effects are also depressive, e.g., a persistent slowing of the EEG waves (227). The mechanism of therapeutic action is unknown, but it is of interest that young animals are highly resistant to electrocution (228), as they are to asphyxia (229, 230).

Less intense currents passed along the neuraxis can produce reflex inexcitability with no preliminary excitation if increased gradually (224, 231). In studies on the frog, Scheminsky's laboratory (232) has consistently found that descending (anode at head) currents depress and ascending ones excite during their passage, with a more or less enduring reversal of action on cessation (233). This has been partially confirmed (86), partially not (80). Such polar action would demand uniformly oriented neural structures or some initial longitudinal polarity of the neuraxis. Evidence for a polarity is seen in the ability of analeptic drugs to lower the threshold for galvanococonvulsion and raise that for galvanonarcosis to just the same extent, while hypnotic drugs alter these thresholds in reverse but still related manner (232). Lapique & Lapique (80, 86) attribute the cord polarity and the attendant peripheral subordination phenomena to an influence of the mesencephalon on the lower neuraxis, an influence which is lost when the midbrain (but not the hemispheres) is cut away and is enhanced when this region is stimulated by picrotoxin.

In the earthworm, however, descending currents in the whole animal or in the nerve cord alone do not simply depress but cause contraction of the longitudinal muscles, while ascending ones contract the circular muscle, and, in both cases alike, excitant and depressant drugs respectively increase or decrease the response (234). Some physiological or anatomical polarization of the nerve cord itself is, however, made probable by these results. Other work on frogs, rats, and dogs has indicated a uniform production of electronarcosis when the current density along the spinal cord



reaches 1 ma. per sq. mm., independently of direction of flow (224, 231). Such currents raise the threshold of the anterior horn cells, as directly tested with microelectrodes. Each of the sensations (flicker, swaying, etc.) evoked by passing weak alternating currents through the human head shows a typical U-shaped intensity-log frequency threshold curve, in most cases with an energy minimum at about 1.5 cycles (235).

It must be apparent even from this too condensed survey of current research (examined through September, 1941) that electric currents in cells and tissues serve in other roles besides that of a natural or artificial stimulus to action. They are also involved in integration of function, metabolism, and growth; in what manner is still largely for the future.

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DEPARTMENT OF PHYSIOLOGY  
UNIVERSITY OF CHICAGO  
CHICAGO, ILLINOIS



## THE SPINAL CORD AND REFLEX ACTION

BY THEODORE C. RUCH

*Laboratory of Physiology, Yale University School of Medicine,  
New Haven, Connecticut*

Previous reviews bearing on this topic (1, 2, 3, 4) were frankly concerned with the central problem of reflex action of the spinal cord—the intimate nature of synaptic conduction. The literature of this type that has since accumulated is scarcely sufficient to warrant a review. For this reason a broader base in subject matter and time has been taken, and the subject of this review might more appropriately be titled "The spinal cord."

*Morphology of the spinal cord.*—Cooper & Sherrington (7) have discovered caudal to a spinal section a chromolysis of large cells in the anterior horns, indistinguishable microscopically from motoneurons, but with the following distinguishing features: (i) the cross-sectional distribution is the ventrolateral border of the anterior horn; (ii) the longitudinal distribution is the twelfth thoracic and the first six lumbosacral segments; (iii) they give rise to fibers which cross the midline to ascend in the ventrolateral white columns (Gowers' tract). This system should be considered in studying the cord potentials from root and tract stimulation. The cell columns in the spinal cord of a human fetus of fourteen weeks has been described by Romanes (5) and of the adult macaque by Reed (6). Holmes & Davenport (8) have enumerated the fibers of the ventral root and the fibers and cell bodies of the dorsal root and its ganglion for all segments of the cat. Peters (9) finds aberrant nerve cells distributed throughout dorsal roots from the cord to the ganglion and numbering three to eighty per root. Section of the dorsal root does not cause chromolysis of the cells in the dorsal root ganglion (six to thirty-five days) in contrast with chromolysis following section of the telodendrons (10).

Required reading for anyone who suspects himself of three-neuron-arc thinking is the description of the intrinsic mechanisms of the spinal cord of the monkey as seen in a region isolated by root and cord sections (11). Even without the distributing system represented by the ramifications of the dorsal root fibers, the remaining internuncial systems constitute a large share of the white and gray matter.



*Morphology of the synapse.*—The literature on boutons terminaux continues to grow, with interest centering around the variations in the morphology of the normal bouton and its distribution over perikarya; and whether degenerating boutons can be distinguished from normal ones with sufficient accuracy to allow determination of the exact termination of tracts. Almost all recent studies emphasize the varied appearance of the normal bouton. Minckler (12), at one extreme, described no less than fifteen classes of boutons in the human spinal cord. These comprise five primary groups which appear in three forms, granular, thickened, and regular. He (13) counts the frequency of each type in relation to age, distribution over cell bodies and dendrites, the gray column of the cord, fixation and autolysis, the latter claimed to be of little importance in contrast with other writers. Barr (14) and Barnard (15) also describe considerable variation in structure and size, some boutons being as large as  $5\mu$  in diameter. Bodian (16) describes the morphology of the synapse (using Mallory-azan stain) in the lower vertebrates and makes functional interpretations. Both he and Barr (14) emphasize that boutons are distributed over certain cells with great regularity and in great density with roughly 40 to 50 per cent of the surface being occupied by boutons.

In a highly controversial paper, Barnard (15) questions whether degenerating boutons can be differentiated from the variations of the normal boutons well enough for tract studies. In fact she appears to claim that boutons show no departure from the normal and do not disappear after section of the parent axon. Even two to five weeks after hemisection her counts gave no evidence that boutons had disappeared, which is certainly a severe indictment of the silver method or else of the neuron theory of the structure of the nervous system! On the other hand, ventral root section caused the boutons on the chromolyzing anterior horn cells to fragment and disappear. The rapidity of postmortem autolysis and the importance of depth of impregnation are confirmed.

The retrograde, transneuronal degeneration described by Barnard has been swiftly re-examined by Barr (17) for spinal nerves, and by Schadewald (18) for the trochlear and abducens nerves. Far from a gross denuding of chromolyzing motoneurons of their boutons, there is no significant difference, statistically demonstrable, in the number of boutons on the cells of origin of neurons with sectioned and unsectioned axons. The upshot is perhaps to empha-



size the need for examining with especial care—prior to publication—experimental results which stand in variance with repeatedly tested and basic generalizations.

It is not impossible that large boutons and other variants in the mammalian spinal cord confusable with degeneration are artefacts due to overimpregnation with consequent blurring of differential features. On the other hand, a light impregnation or a histologic stain may disclose too few boutons or be too random in its action to make the bouton method safe for tract studies; it may nevertheless give valuable information. Three papers which seem never to appear in the bouton-lineage are those of Rasdolsky, who in 1923 studied bouton degeneration with fuchsin stain following lesions of the motor areas, spinal hemisections, and dorsal root sections (19, 20, 21). He is perhaps the first to study bouton degeneration in detail, and it is interesting that he used a dye rather than a silver method.

*Internuncial activity.*—In view of the increasing interest in internuncial activity, particular importance attaches to Renshaw's (22) isolation of the two-neuron-arc component of the ipsilateral flexion reflex. This reflex is a valuable tool for the analysis of synaptic events, and by subtractive reasoning aids in allocating the responsibilities of the internuncial system as yet too complex for detailed analysis. Following stimulation of a dorsal root there occurs a ventral root discharge with a minimal reduced reflex time of 0.65 msec., which in agreement with Eccles & Sherrington's (23) original determination is reduced to 0.5 msec. by facilitation. These durations coincide with the measurement of synaptic delay of motoneurons by the method introduced by Lorente de N6 (24), which involves stimulating the electrodes inserted into the gray matter and measuring the time elapsing between discharge of directly activated motoneurons and those activated through a synapse. Unquestionably the earliest phase of discharge from ipsilateral stimulation occurs with a synaptic delay which precludes passage of more than one synapse, and must therefore represent the activity of collaterals of dorsal root fibers which Cajal describes as passing without interruption to the anterior horn. Discharges due to impulses arriving at motoneurons via internuncials can also be identified.

The manner in which the pyramidal pathways activate the motoneuron pools of the spinal cord has been analyzed by Lloyd



(25), using microscillographic leads from various areas of the gray columns. The pyramids are stimulated after section of all other pathways below and all pathways above. A single pyramidal volley is subject to considerable temporal dispersion in passing down the cord, some fibers conducting at 63.5 m. per sec. while others conduct at an estimated 18 m. per sec. There exists then in the conduction properties of the tract a potential basis for temporal summation without the necessity for temporal summation at synapses, since the slow impulses of a first volley arrive coincidentally with the fast impulses of a second volley.

The earliest areas of the gray matter to become active are (i) the external basilar region, i.e., the extreme lateral margin of the base of the dorsal horn, and (ii) the solitary cells (Lenhossék) of the dorsal horn. In response to repetitive stimulation but not to single volleys the intermediate region of the gray matter becomes active after a latency of 12 to 20 msec. The intermediate region appears to contain the "premotoneuron" internuncial relays, and in general to be excited from the basilar elements, though evidence of a more direct connection with pyramidal tract fibers is sometimes encountered. Motoneuron facilitation, tested by means of the two-neuron reflex arc discharge, parallels the potential of the intermediate region and is marked by the same *addition latente*. Facilitation at the internuncial level, tested by the effect of pyramidal discharge on the three-neuron components of the ipsilateral reflex, occurs slightly earlier than motoneuron facilitation. Since it is the discharge of the intermediate nucleus which facilitates motoneurons, the interval is the "nuclear delay" of the intermediate nucleus. In some instances the activity of the intermediate region is suspended by pyramidal discharge suggesting that the locus of reciprocal innervation lies in the premotoneuron internuncial system. In the pathway of excitation from the dorsal root there seems to be no intercalated system upstream to the intermediate region.

The mode of activation of internuncial systems by stimulation of the ventral white columns has also been studied in great detail by Lloyd (26) but the subject does not lend itself to brief description.

*Inhibition.*—The fruitful concept of Gasser that reflex inhibition is related to the subnormality-positivity phase of some element of the reflex arc (internuncials) continues to exert a healthy influence on an old controversy by providing a true alternative to



the earlier concept of Sherrington. The alternatives are broadly reducible to the catch phrases "activity deficit deriving from preceding activity in the same neurons" and "specific inhibitory processes or terminations." An interconnected theme is the locus of inhibition, internuncial or motoneuronal, since the latter puts great strain on the first hypothesis.

McCouch, Hughes & Stewart continue their analysis of the cord potentials of inhibited reflexes. In the earlier study (27) the first negative crest of the premotoneuron or intermediate potential from ipsilateral stimulation was reduced by contralateral (inhibitory) stimulation, and to the same degree that reflex contraction is reduced, suggesting an internuncial locus of inhibition. Inhibitory deficit in the myographic contraction was roughly proportional to the depth of positivity found by the testing volley. New evidence gained from a study of the restricted potentials of the spinal monkey (28, 29, 30) is that, if the conditioning volley gives rise only to negativity, only refractoriness of internuncials is seen, i.e., a deficit in the cord potential of the testing volley for intervals up to 20 to 25 msec. Prolonged unresponsiveness is related to the development of the positive wave from the conditioning volley. Positivity and negativity are dissociable. Positivity becomes more pronounced as the animal recovers from spinal shock. Positivity is not increased by repetitive stimulation, as is the case in peripheral nerve; a perikaryal origin is thus suggested.

In crossed inhibition of the flexor reflex (31) again prominence of the positive wave and depth and persistence of inhibition are associated, both increasing with the interval after transection. In cats with chronic spinal shock, the reduction of cord potential by crossed inhibition parallels the reduction of reflex contraction. But when spinal shock is at its height the motoneuron discharge is more inhibited than the cord potential, which may entirely escape. For the cord potential to escape, presumably means that inhibition has occurred in some other way than in altering the internuncial drive upon the motoneurons. Thus evidence is being built up for inhibition associated with positivity, for inhibition occurring both at internuncials and motoneurons and for a perikaryal contribution to the cord potential.

Renshaw (32) has demonstrated an inhibition-like effect of antidromic volleys upon adjacent, reflexively activated motoneurons. Spatial contiguity of the exciting and excited motoneurons is a fac-



tor, since nerve branches to the same muscle give the best results. The response deficit is maximal when the testing impulses are set up shortly after the antidromic volley is initiated and gradually decreases to disappear at 45 to 50 msec. When the two-neuron reflex arc is used, it is found that "inhibition" occurs when the antidromic and testing volleys arrive simultaneously at the motoneuron, i.e., at the beginning of the period of synaptic delay. Thus motoneurons are subject to "inhibition" without antecedent activity. It would seem important to resolve the alternatives suggested by the author: (i) a synaptic phenomenon employing recurrent collaterals, i.e., axonic branches of motoneurons which terminate on other ventral horn elements; or (ii) a polarizing action of the antidromic action current.

The two-neuron reflex arc (22) as studied by Lloyd (33) has proved extremely valuable in testing theories of inhibition because internuncial activity need not be considered. The fact that a two-neuron reflex arc is subject to inhibition from afferent stimulation is in itself suggestive of a direct inhibitory action on motoneurons so that the time relations are critical. Noticeable inhibition occurs when conditioning and testing shocks are delivered simultaneously and deepens to a maximum when the inhibiting volley leads by about 0.7 msec., after which it lessens and passes over into facilitation. The actual duration of inhibition is clouded by the advent of impulses over three-neuron arcs with resultant facilitation. For inhibition to occur from simultaneously initiated volleys precludes any synaptic crossing before the motoneuron is reached. Such inhibition cannot be explained by any interplay of internuncials. Therefore the action is one of the primary dorsal root fibers through their collaterals on the motoneuron. The phenomenon is not ascribable to "blocking" of impulses in the dorsal columns (Barron & Matthews), since the collaterals of the ventrolateral column fibers with a spatially opposite orientation show a similar inhibitory effect.

From several sources evidence is accumulating that nerve impulses, incident at anterior horn cells, exert a depressor activity other than the sequelae of the detonator action. Such a phenomenon can be based on precedent activity, only if the activity is sub-threshold (for the motoneurons), i.e., activity differing only in time relations of incident bouton discharges or some unknown way from activity which leads to the discharge of the motoneuron.



Otherwise postulation of a specific inhibitory action seems justified. McCouch (31) suggests the term "inhibition" be used in this restricted sense and "extinction" be used for depression of excitability following discharge of nerve impulses. Or, of course, inhibition can be retained in the generic sense to mean no more than a depression of neuron discharge as a result of afferent (*sensu lat.*) impulses and qualified by appropriate adjectives as our knowledge progresses, just as we now distinguish two phenomena by "central" and "peripheral" inhibition.

*Dorsal root discharge and related phenomena.*—The "recurrent discharge" over dorsal roots (34) is no longer ascribed to recurrent collaterals of neurons having their cells of origin in spinal ganglia of adjacent segments (35). Rootlets demonstrated to carry the discharge when sectioned show no degeneration in the distal portion. Section of the dorsal columns above the stimulated and recorded rootlet ends the phenomenon. Two fibers and cross excitation are therefore postulated but no satisfactory explanation of the absence of delay, etc. is offered.

If the dorsal roots discharge centrifugally in response to stimulation of other dorsal roots (Toennies), impulses should also pass up the ascending branches of the discharging fibers and be detectable by recording from the posterior columns. Following in the wake of the primary sensory impulses in the posterior columns, a second wave, travelling at the same rate and in the same lamina of fibers, has been recorded by Hursh (36); like Toennies' dorsal root discharge it suffers reduction by a preceding volley and has a latency of about the same order (*ca.* 2.4 msec.). The phenomenon is favored by cooling but occurs at normal body temperatures. Renshaw & Therman (37), stimulating and leading from two divisions of the same dorsal root, record a potential preceding the Toennies discharge which occurs only when the dorsal columns are sectioned a few millimeters above the root entry zone. Analysis indicates that the discharge is mediated by antidromic conduction over the ascending branches of dorsal root fibers which are excited by the spike negativity of adjacent ascending collaterals at the site of the cord section. Impulses descending from the point of section enter the segmental collaterals and increase reflex responses. The phenomenon is fugitive, lasting from a few seconds to thirty minutes, and is favored by cooling.

This phenomenon has value as a model of synaptic conduction



in suggesting that impulses may modify the activity of adjacent axons or motoneurons without synaptic connection; Renshaw's finding may explain why spinal shock requires a few minutes to reach maximal effectiveness, though it can hardly be more than an artefact in the Sherrington-Sowton phenomenon or the Schiff-Sherrington phenomenon. Experiments of this type prompt the thought that a certain preciousness unworthy of the great technical virtuosity is creeping into the oscillographic studies of the spinal cord. Phenomena lasting only a few minutes, facilitated by cooling, restricted to topographically adjacent fibers and presumably occurring only in response to unphysiological synchronous volleys, though of analytic value, can scarcely play a part in normal function. Dorsal root discharges may prove a keystone, or to be a scientific curiosity.

*Delayed effects of asphyxia.*—Van Harreveld & Marmont (38) and Häggqvist in Sweden (39) have independently investigated the delayed effects of asphyxia of the spinal cord, a subject of current importance in aviation physiology. The first workers have made a definite methodological advance over the Steno procedure in using a principle employed by Cushing, i.e., of raising the pressure inside the vertebral canal above blood pressure by forcing saline into the sac formed by ligating the cord at the sixth to tenth thoracic segments. Unlike previous workers both are interested in the effects manifested after relief of the ischemia.

Van Harreveld & Marmont (38) find that prolonged asphyxia (lasting 75 min.) abolishes reflex action permanently; after 55 to 65 min. of ischemia, tendon reflexes and extensor "tone," often excessive and accompanied by clonus, appear after an interval of areflexia and persist for a period of one or two days and then disappear permanently. After shorter periods exaggerated extensor reflexes return and persist at a level comparable to decerebrate rigidity while flexion reflexes are absent or hypoactive; shorter periods (25 min.) are without definite effect. Extensor hyperactivity is interpreted to mean that "a functional system which normally inhibits the reflex activity of the spinal cord is abolished by asphyxia, releasing the excitatory activity of the cord." The diminished flexor activity is ignored.

In a second paper (40) many of the obvious shortcomings of the first are overcome, e.g., inhibition of the knee jerk from ipsilateral stimulation is directly studied myographically. Inhibition fails



when ipsilateral flexion fails and often when flexion occurs. Co-contraction sometimes occurs and the conclusion that reciprocal innervation had been abolished is drawn without sufficient regard for the phenomenon of concealed and dominant reflexes. The conclusion that inhibitory "structures" are preferentially affected by asphyxia can scarcely be reached until the inhibitability of the flexor reflex is also studied. Asphyxiation without ligation induces hyperalgesia in the segmnets affected (41). The average duration of asphyxia (transection of the aorta) necessary to abolish all reflex activity in spinal cats is 3 min. 22 sec., as a delayed effect of partial asphyxia this figure is increased to 11 min. (42); observations relating to spinal shock are discussed elsewhere.

According to Häggqvist (39) constriction of the abdominal aorta for 15 to 25 min. induces in the rabbit a permanent spastic paresis-in-flexion of the hind limbs and degeneration of larger motoneurons, while the smaller anterior horn cells and their axons in the root are largely spared. He explains the spastic paralysis by a hypothesis of dual innervation based on extensive counts of fibers by diameter, namely, a large fibered ( $10\mu$ ) contractile innervation with terminations "*en plaque*" and a small fibered ( $4\mu$ ) "tonic" innervation with terminations "*en grappe*." It seems scarcely necessary to criticize the protean theory of dual innervation each time and for each shape in which it arises until the following criterion is met: normal muscle must be considered capable of only one kind of activity—contraction—when innervated via the central nervous system until other types (tonic) of response can be demonstrated by nerve stimulation with rates and other characteristics of proved physiological order. Moreover the Sherrington theory of the reflex nature of "tone" is of sufficient stature to require disproof by direct experimentation before other explanations can be convincing.

*Spinal shock.*—The problem of the intimate nature of spinal shock is receiving something of the attention warranted by the importance of the subject. Because it has not been touched on by previous reviewers it will be treated more fully. Since Sherrington's well known analysis little advance has been made until the last five or six years. In 1934, Liddell (43), utilizing modern conceptions published a masterful exposition of Sherrington's hypothesis, which relates shock to a withdrawal of facilitation from prespinal levels. However, inhibition has also played a large part in theories of spinal shock beginning with Goltz, who ascribed it to an irrita-



tion of descending inhibitory pathways. The knee jerk is more susceptible to ipsilateral inhibition in the spinal than in the decerebrate state (44) and the failure of the crossed extensor reflex and stretch reflex (45) may in part be due to the overactivity of the inhibitory side of a concealed reflex (crossed flexion and lengthening reaction respectively). With lapse of time after transection the knee jerk becomes less easily inhibited and may not be dissimilar in this respect to the decerebrate reflex (46). This is interpreted by Liddell in terms of the altered state of the motoneurons whereby they become more subject to inhibition just as they are less excitable, and not as a release of inhibition. The reviewer (47) has stressed the dangers in framing generalizations about the spinal and decerebrate state from observations of the excitability of only one type of reflex, flexor or extensor. Caudal to a spinal transection in the decerebrate animal, flexor and extensor reflexes are affected oppositely. Cephalad the change is also reciprocal between flexors and extensors and opposite in sign to the changes below the level of the lesion. This is traced to a reciprocal action of the long tracts either by reciprocal innervation of the motoneurons or by facilitation of reciprocally acting interneurons. The former is suggested insofar as extensor reflexes as a class, regardless of the afferent source, are less active while flexor reflexes become overactive. Some newer evidence points to the internuncials as the site of spinal shock though not exclusively so. In a series of analytical papers, McCouch, Hughes & Stewart (28, 29, 30, 31) report studies utilizing the cord potentials to analyze the state of reflexes in shock and after recovery in two degrees of severity, cat and monkey. Evidences of depressed activity of the internuncial system are: (i) decrease of the cord potential up and down the cord in the chronic over the acute state and in cat over monkey; (ii) absence of positivity in acute spinal cat, which fails to correlate with enhanced ipsilateral inhibition; and (iii) the internuncial potentials are at first confined to the ipsilateral side which with other evidence suggests an unresponsiveness of the dendrites of internuncials. A recent paper (31) fills the need for a study of the crossed inhibition of the flexor reflex to parallel the knee jerk studies. The depth and duration of inhibition of the flexor reflex increases with the interval after transection though, as is well known, the excitability of this reflex *increases* with recovery. During deep shock (acute in the cat and chronic in the monkey) the reflex contraction may be



deeply inhibited with very little reduction of the internuncial potential but as shock lessens cord potential and the reflex are more equally inhibited. Crossed inhibition suffers and recovers from shock much as does the crossed excitation of extensor muscles as would be expected if descending tracts terminate upstream to the locus of reciprocal innervation. Susceptibility of the motoneuron to inhibition is also a factor but not the only one.

Van Harreveld (48) has proposed a new inhibitory theory of spinal shock based on the fact that a short period of ischemia of the cord causes the state of nearly complete areflexia of the spinal monkey to give way after an interval of one or two days to one of enhanced activity. Extensor reflexes, including "tone," tended to recover before reflexes from the skin, but the enhancement is more temporary, lasting from a few hours to two days before giving way to complete areflexia. A gauge of the degree of activity is that a stretch reflex was recorded. These experiments recall the similar though slighter action of ephedrine (49) in diminishing spinal shock. Van Harreveld however takes the fact "that asphyxia of the cord curtails spinal shock to mean that it is due to a dominance of a spinal inhibitory mechanism, which is more sensitive to asphyxia than the excitatory structures in the cord"; the inhibitory mechanism is released by transection from a normally depressing discharge from the brain. It is unfortunate this formulation should be expressed in terms (i.e., excitatory and inhibitory structures), which convey little, at least to the reviewer. The delay, in appearance and the duration, of the hyperreflexia does not without direct proof seem adequate for ruling out increased excitability as a consequence of asphyxia, nor is the fact that an immediate "release" of certain reflexes following transection accounted for. Finally, as McCouch *et al.* (31) have shown, crossed inhibition of the flexion reflex is depressed, not released by transection, which is contrary to the fundamental postulate in van Harreveld's theory.

Several descriptive studies of the striking areflexia of the spinal monkey have appeared. Hinsey & Markee (50) have given a detailed description of the time of appearance and the recovery of various somatic reflexes with comparisons of other forms. Van Rijnberk & ten Cate (51, 52, 53, 54, 55) have described tail, abdominal, cremasteric, and other reflexes of the genital region of the dog. Sahs & Fulton (56) have studied after transection of the cord in the monkey the reflex arcs underlying the drop in temperature



of the foot when the other foot is immersed in ice water. Though there is a tendency to lump all autonomic reflexes together as phylogenetically old and hence "spinal," they show that not only are such reflexes subject to profound spinal shock, but that some are more dependent on higher levels than many somatic reflexes.

Fulton & McCouch (57) provide further evidence of the importance of the corticospinal component of a total spinal section. If ablation of the motor cortex or hemidecerebration is followed by a total transverse section of the spinal cord, reflexes recover more quickly on the side opposite the cortical procedure. Such asymmetry is greater in the higher than lower primates and is in evidence in some degree for several months. After spinal section recovery of reflexes progresses in a distal to proximal order, while the reverse order holds after cortical ablation.

On the whole, Sherrington's original formulation as amplified by Liddell (43) seems adequate if the reciprocal nature of reflex changes after spinal transection is recognized and the action of descending tracts on both motoneurons and internuncials be taken into account. Withdrawal of facilitation explains decreased excitability and increased inhibitability. However, it is questionable whether the above cited studies really attack the problem of the intimate nature of spinal shock and especially of the mechanisms underlying recovery. One may ask whether the interruption of the spinal cord or anterolateral columns of a decerebrate animal is comparable to terminating a low-grade repetitive nerve stimulation, facilitatory and inhibitory to given reflexes. If so, the difficulties are simply transferred to the problem of what causes reflexes to return with lapse of time. On the other hand, spinal shock can be considered to be something due to the withdrawal of facilitation, but disruptive as well as subtractive, so that recovery becomes merely a return of normal reactive abilities. Spinal shock in this restricted sense could be a slighter but parallel phenomenon to transneuronal degeneration, sufficient for a functional but not necessarily histologically detectable damage. At one time it looked as though the phenomenon of "isolation-dystrophy" of peripheral nerves and muscles pointed in this direction, but this appears to be a mechanical damage to the sciatic nerve resulting from the abnormal sitting-posture of the spinal monkey (7, 11, 50, 57, 58, 59). Also against such a point of view is Tower's important demonstration (11, 60) that the internuncials and motoneurons suffer little



anatomic damage when completely isolated from all nerve impulses by combined cephalad and caudal transections and sections of the intervening roots. But function rather than histology is the criterion and it would be instructive to study the excitability to direct stimulation of the cell bodies of the lateral geniculate body while undergoing transneuronal degeneration from section of the optic tracts.

*Reorganization after nerve crossing and muscle transplantation.*—Sperry (61), using the rat, finds no functional readjustment of foot movements, either immediately or after opportunity for retraining, to interchange of flexor and extensor muscles of the foot; this was true for ordinary cage activities and after a variety of conditions calculated to favor readjustment. Similar reversed movements obtain in nerve crossing experiments (62), in which muscle branches to the soleus and tibialis anterior muscles rather than compound nerves were crossed, all other muscles of the lower leg being excised. When compound nerves (peroneal and popliteal) are crossed, the foot movements are not reversed, but are abnormal, with plantar flexion predominating; re-education is not apparent. These results controvert most previous work, but a cogent critique is offered.

Watrous & Olmsted (63) have addressed themselves to the question whether adjustment to nerve crossing alters the basic reflexes of the decerebrate cat and dog. After crossing the nerves to the tibialis anterior and gastrocnemius and allowing time for recovery, reflexes of isolated muscles to nerve stimulation were recorded isotonicity. A pure reversal, with reversed reciprocal relations, does not obtain; rather the response is one of cocontraction, which the authors believe occurs in a degree beyond that ascribable to concealed reflexes and normal to the decerebrate animal. The whole interpretation swings on the validity of this assumption. Section and resuturing, without crossing, produces somewhat similar cocontractions, the phenomenon of "despecification." Thus the tibialis anterior yields quite large isotonic responses to crossed stimulation; flexor ipsilateral reflexes are little altered. Despecification and remodulation are obviously superficially similar and difficult to separate, and the argument cannot be given here. The end result appears to be that after nerve crossing extensors muscles innervated by a "flexor" nerve contracts to contralateral stimulation and flexor responses are inhibited, though the nerve to the flexor



muscle (popliteal), before crossing, carries the discharge in the crossed extensor reflex: ipsilateral reflexes are not subject to the same readjustment. That any re-education can occur as a brain-stem and cord function is surprising. A result so radical as this warrants repeated scrutiny. In earlier experiments (64) an extensor muscle transplanted to a flexor position, without removing the normal flexor, behaved after decerebration following on a period of recovery as though it had never been transplanted. The reverse experiment in the limb and transposition of the superior oblique muscle of the rabbit were similar in result.

*Action of drugs, electrolytes, etc., on reflex action.*—Merlis & Lawson (65) have introduced a well conceived technique for studying the action of pharmacological agents, electrolytes, etc. on the spinal cord, which consists of perfusing the subarachnoid spaces with solutions at constant pressure and temperature. Experiments on physostigmine made with appropriate controls to delimit the site of action show that this substance induces, not an all-over enhancement, but has a preponderant depressant effect on the knee jerk, and a consistently augmentary action on ipsilateral flexion and contralateral extension reflex. The importance of examining antagonistic reflexes and crossed as well as ipsilateral reflexes (see above) is illustrated. Intravenous and intracarotid injections of physostigmine and acetylcholine give complex effects on reflex action with indications of several peripheral and central sites of action (66).

An analysis (67) of the effects of serum magnesium on reflex actions of the spinal cord indicates that reflex failure is determined by a peripheral action which is to block nerve-muscle twitches before tetani, and slow tetani before rapid ones. The serum concentration at which various spinal reflexes fail differs markedly and correlates with their known rates of central discharge. Perfusion of the subarachnoid spaces of the spinal cord with an artificial cerebrospinal fluid, calcium-free or with citrate added augments the ipsilateral flexion reflex and causes "spontaneous" twitching of the musculature of the appropriate segments (68). The latter on analysis proves to be not "spontaneous" but of reflex origin, though this is not entirely so for citrate experiments.



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LABORATORY OF PHYSIOLOGY  
YALE UNIVERSITY SCHOOL OF MEDICINE  
NEW HAVEN, CONNECTICUT



## THE CENTRAL NERVOUS SYSTEM

BY MARION HINES

*Department of Anatomy, Johns Hopkins University,  
Baltimore, Maryland*

A review such as this, of the literature published between July 1, 1940, and June 30, 1941, on the anatomy and physiology of the central nervous system, can achieve a semblance of unity only through regional classification. Consequently the investigations reported are grouped according to the division of the central nervous system with which they are concerned. Discussion either of results or of conclusions is precluded by the space assigned. Nevertheless, wherever possible, comment has indicated the relation of results and conclusions to the present state of our knowledge of the subject under investigation. Much of the published work of this twelve-month period bristles with unorthodox findings and should therefore prove an adequate stimulus for new patterns of activity in the central nervous system of man himself.

### ONTOGENETIC DEVELOPMENT OF ACTIVITY IN THE CENTRAL NERVOUS SYSTEM

In his review on the functional development of mammalian neuromuscular mechanisms, Barron (1) suggests that the two divergent views of development of activity can be laid to the species difference studied by particular authors. The first of these views, i.e., that particularized reflex behavior develops out of more generalized forms, is illustrated by Youngstrom's descriptions of the development of two different somatic motor innervations in larval amblystoma (2). The primary motor cell, which as the name implies is the earliest to appear, can by its anatomical relations effect Coghill's generalized response. The secondary motor cell which develops later is first seen in the cephalward levels of the spinal cord and can by its neurononic connections effect only localized responses. Since these two cells existed simultaneously, Youngstrom postulated a double innervation of musculature, although he offered no proof of a double innervation of a single muscle fiber.

As a contrast to the early development in amblystoma,



Barron's own studies illustrate the second view of early development of functional activity, namely, that patterned activity emerges out of simple, stereotyped reflexes. In fetal sheep Barron finds three phases of reflex development. In the first phase of simple reflex activity (40 to 50 days gestation) all movements are jerkily performed, respiration is gasping, and postural reflexes are confined to tonic neck reflexes and to the effect of eyes upon the extremities. In the second phase (46 to 75 days) movements are sustained, showing rigidity in the latter days, respiration is continuous, and head and body righting appears. In the last phase (55 or 62 to 85 or more days) movement, respiration, and postural reflexes are inhibited. Further, Barron correlated these three phases of development of reflexes with the stages in maturation of the muscle spindle. At forty-seven days the spindle was well formed. In the sheep early nervous activity begins in the region of the lower medulla oblongata and the upper medulla spinalis and progresses both caudalward and cephalward. And as the maturation of the central nervous system progresses, simple stereotyped reflexes of this region give way to more complex types of patterned activity which involve the development of more cephalward and caudalward levels of the neuraxis.

#### THE NEURAXIS

*The spinal cord.*—The intimate relation of neuron to neuron has been reinvestigated with histological as well as neurological techniques by Bodian (3). Bodian described the terminations of axons on the nerve cells of the tegmentum and of the cerebellum in the goldfish, the cat, and the monkey. In the goldfish the smallest terminals were  $0.5\ \mu$  in diameter; the largest,  $7.0\ \mu$ . The larger terminals were adherent to the cell body, and the smaller ones were distributed over the perikarya, on the dendrites, and on the proximal parts of the axon. The smallest endings were those of nonmedullated fibers. The distance between these small terminals was about that of the width of the terminal itself. In the mammals studied, the terminals were separated on the surface of the neuron by the supporting feet of neuroglia cells. When fixed with Regaud's fluid and differentially stained, all endings appeared to contain accumulations of mitochondria near the terminal membrane. The terminal membrane and that of the receptive cell were so closely adherent that only one was seen. The finding of



multitudes of terminals on the axon hillock and on the axon itself give pause to the generally accepted notion that the impulse only passes from dendrite to axon.

The hope that degeneration of terminals of specific axons could be used to analyze relation of particular fiber tracts to particular groups of nerve cells falls before the careful work of Barnard (4). The end feet on the cells of the ventral horn of the cat's spinal cord measured  $0.5 \mu \times 0.5 \mu$  to  $3.0 \mu \times 0.5 \mu$  when impregnated by Cajal's silver method, but when fixed by Regaud's fluid and stained by histological techniques, these terminals did not vary greatly in size, measuring about  $1 \mu$  in diameter. If fixation after death were delayed for twenty-five minutes, fragmentation of the end feet was marked; if delayed for forty minutes, only granules and debris were present. Cutting the dorsal roots, hemisection of the spinal cord, and removal of the motor cortex in cats were not followed by any marked decrease in number of end feet on nerve cells in the spinal cord; but strangely enough, when the ventral roots were severed, the end feet on the chromatolyzed anterior horn cells fragmented and disappeared.

On the other hand, Schadewald (5) cut the trochlear and abducens nerves in cats and found no change in the end bulbs on their cells of origin in spite of the fact that the numbers and sizes of the end feet were of the same order as those found about the somatic motor cells in the spinal cord. Minkler (6) studied the distribution of nerve terminals in the human spinal cord of individuals ranging in age from ten months to eighty-three years. The end feet were similar regardless of age if similar nuclear groups were examined, although different types may be found on the same nerve cell. Contrary to Barnard's report, he considered that autolytic processes during the first twenty-four hours did not change the morphology of the end feet to any great degree. The technique used and the animals studied were dissimilar. Certainly, fixation plays a role, and that used for study of end feet by some of the earlier investigators was chloral hydrate—a fluid used in histological techniques for slow maceration.

Cooper & Sherrington's (7) finding of chromatolysis in nerve cells which bound the periphery of the nuclear groups in the ventral horn of the monkey's spinal cord contralateral to a hemisection does more than call into question the previous allocation of origin of Gowers' tract only to nerve cells in the Clarke-Stilling



column. Since these cells are indistinguishable from ventral horn cells, which are known to be motor in function, this finding calls for a reinvestigation of the nuclear groups within the ventral horn, not only of the monkey but also of other animals. The old classification of all nerve cells within the basal plate as the cell bodies of motor nerves undoubtedly needs revision.

Lately, Lassek (8, 9, 10) has concerned himself with the origin of the pyramidal tract in man and in the monkey, finding that the Betz cells of layer V in area 4 can account for only about 2 to 3 percent of the axis cylinders in the pyramidal tract (at the decussation) in man and between 3 and 4 per cent in the monkey. He also noted that small fibers predominated in the tract itself. Carefully measuring six thousand of the pyramidal cells in area 4 in man, he found pyramidal cells to have areas of 200 to 4,100 sq.  $\mu$ , the largest being in the leg area. Since the time of Holmes and Page May the origin of the pyramidal tract has been enlarged to include not only deep cells in layer III of area 4 but also cells in the post-central gyrus (note results of Brooks & Woolsey, p. 390). Furthermore, Eöonomo & Koskinas, who have measured the size of nerve cells in three dimensions in all layers of the whole of man's cerebral mantle, found that the largest cells in layer V of area 4 (para-central lobule) had an area 1.7 times that of the largest cells tabulated by Lassek.

The section of the lateral funiculus of the spinal cord (at the fourth cervical segment) in two stages (11) as treatment for tremor in unilateral paralysis agitans made an interesting contribution to the understanding of the function of that portion of the spinal cord in man, providing that the initial lesion was not subsequently enlarged by the processes of repair. Apparently severing the spinocerebellar pathways did not interfere with the development of clonus or of brisk, irradiating reflexes. Although the gait was hemiparetic, the interruption of a greater number of nerve fibers at the second operation conferred upon the patient a better ability to walk. Further, no rigidity on passive motion was observed—a finding which calls for a reconsideration of the relative contribution of the old and new motor systems to tone in skeletal muscle. The fact that the fingers on the side of operation could be moved individually suggests that in this particular patient the pyramidal fibers for the leg may have been placed dorsally to those destined for the hand. Knowledge of topographical localiza-



tion within the pyramidal tract as it passes through the lateral funiculus is wanting.

*Medulla oblongata.*—To find four papers published within a single year dealing with the distribution of primary or secondary neurons of afferent systems within the medulla oblongata is rare. The function of the mesencephalic root in the cat at last is settled. Corbin & Harrison (12) found it to contain afferent fibers from the muscles of mastication which respond to stretch, and from the teeth and gums, which respond to pressure. No stretch receptors from the extraocular muscles enter the root.

Schwartz & O'Leary (13) were able to cut the tractus spinothalamicus lateralis and the descending root of the spinal fifth tract in surgical intervention for intractable pain. This procedure allowed them to conclude that the lowest dermatomes were represented dorsolaterally and the upper, ventromedially in the tract, and that the mandibular division of the portio major was found ventrally in the descending root. Pain and tickling sensation were both affected.

Studying the development of the tractus solitarius in embryos of man, sheep, rat, and cat, Wilson, Windle & Fitzgerald (14) have added to the doubt, already significant, that the nucleus and tractus solitarius are purely visceral sensory. Although only the axons from the petrosal and nodose ganglia formed the tract in the younger embryos, later (15 mm.) axis cylinders from the superior and jugular ganglia and those from the eleventh nerve entered to form the tract. The fibers of the tract itself not only terminated in the nucleus solitarius and in or near the motor nucleus of the seventh nerve but also descended into the dorsal funiculus of the spinal cord of the same and opposite side to end in the sheep and man at the level of C<sub>1</sub>, in the rat at C<sub>4</sub>, and in the cat at C<sub>6</sub>.

A discretely placed lesion of the medial vestibular nucleus (15) was followed by descending degeneration (i) of the fasciculus longitudinalis medialis, which continued into the ventral funiculus of the spinal cord, (ii) of the tractus vestibulospinalis on the same and opposite side (greater on the same side), and (iii) of fibers in the reticular formation on the same side. The ascending degeneration (i) of the fasciculus longitudinalis medialis was followed bilaterally to the level of the oculomotor nucleus, and that (ii) of reticular fibers to the level of the troclear nucleus. No degenerating



fibers were traced to the nucleus ruber or to any thalamic nuclei.

The lesion was followed by nystagmus (both spontaneous and induced), postural abnormalities, kinetic deviations to the side of the lesion, diminution of tendon reflexes and of grasping, loss of righting reactions on the side of the lesion, as well as ipsilateral and occasionally contralateral hypotonia. Hitherto, contribution of fibers to the medial longitudinal fasciculus or to the tractus vestibulospinalis by the medial vestibular nucleus has been considered doubtful by many investigators (except Winkler).

*The thalamus: the dorsal thalamus and subthalamus.*—The anatomy of some part of the dorsal thalamus was investigated in forms as divergent as teleosts, marsupials, and primates. In the teleost (16) the four general divisions of the diencephalon, epithalamus, dorsal thalamus, ventral thalamus, and hypothalamus, were arranged in horizontal zones—the basic organization of this part of the vertebrate nervous system is not so clearly visible in higher forms.

Goldby (17) investigated the nuclear masses of the dorsal thalamus in the marsupial, phalanger, as a preliminary to experimental work. The midline nuclei were numerous and well outlined, and those of the lateral division were more definite than homologous areas in the opossum. The dorsal nucleus of the lateral geniculate body was laminated, a small pulvinar was identified, the ventral nucleus had three subdivisions, and the medial nucleus showed some lateral differentiation.

Although the differentiation of the lateral division of the dorsal thalamus is well known in man, any study which allows a better understanding of the termination of different systems is welcome. Papez *et al.* (18) were able to add to the certainty of our knowledge of terminations of three thalamicopetal systems in the brain of a patient with marked atrophy of the dorsal thalamus. The nuclei ventroposterior et ventrolateralis received the spinal and medial lemnisci, the terminals of the brachium conjunctivum, the fasciculi thalamicus et intrathalamicus. In particular the proprioceptive and general cutaneous terminals (for the body) overlapped widely in the nucleus ventroposterior; the cerebello-thalamic fibers ended in the nucleus ventrolateralis and in the nucleus medial centralis, while the general cutaneous sensibility from the face (trigeminal lemniscus) terminated in the arcuate nucleus.

In his recent investigation of the medial nucleus in the ma-



caque, Walker (19) found no direct connections with primary receptive areas for any type of sensibility. Rather, that nucleus was related on the afferent side to nuclei of the thalamic midline and the hypothalamus, to the lateral thalamic nuclei, to the centre median, and to the prefrontal cortex. The medial nucleus sent efferent fibers to the prefrontal cortex and to the hypothalamus. Contrary, therefore, to the findings of earlier investigators of this nucleus in both man and other primates, no fiber connections with any part of the corpus striatum were described.

The few isolated cases of hemorrhage into the subthalamic nucleus of man have contributed little to an understanding of its function. It is helpful then to discover an interest in direct stimulation of the subthalamus which the Clark-Horsley apparatus makes possible. Waller (20) found a locomotor point in Forel's field at the level of the subthalamic decussation near the nucleus subthalamicus. Stimulation of this area in cats elicited rhythmic movements of the legs, smoothly executed, the forelegs leading. There was a latent period of two to three seconds, and the movements continued as long as the stimulus endured, ceasing with the stimulus unless the anesthesia was very light.

*The thalamus: the hypothalamus.*—The use of the Clark-Horsley apparatus continues to allow investigators to probe the hypothalamus and attempt exposure of its function by direct electrical stimulation or by discrete lesion. The hypothalamus contains three distinct regions; namely, (i) that of the area dorsal to the optic chiasma, containing the supraoptic nuclei, (ii) that of the tuber cinereum, containing the dorsal, ventral, and posterior hypothalamic nuclei, and (iii) that of the corpus mamillare with its several nuclei. Anterior to the hypothalamus proper, lying in the telencephalon medium, bounded anteriorly by the lamina terminalis and posteriorly by the preoptic recess, lie the preoptic nuclei. For convenience studies of the preoptic area will be considered with those of the hypothalamus proper.

Consideration of the investigations of this whole region falls into three groups, as follows: (i) relation of this region to the function of the glands of internal secretion, (ii) relation of this region (a) to control of organs innervated by the autonomic nervous system and (b) to control of heat regulation, and (iii) studies of the peculiar secretory-like nerve cells which characterize the preoptic area.

With a lesion which may have destroyed the nerve fibers from



supraoptic nuclei to the hypophysis, ovariectomized guinea pigs failed to respond to previously effective doses of estrogen and progesterone (21). This was interpreted as a result of destruction of that part of the central nervous system which is indispensable for the integration of behavior patterns. Lesion within the more ventral portion of the walls of the tuber cinereum of rats (22) was followed by a stormy convalescent period in which temperature regulation was disturbed and the rat refused to eat and to drink. All animals which survived doubled their body weight due in part at least to a great increase in extractable lipoids. This increase in adiposity was accompanied by definite malnutrition of the skin and by a sex dystrophy as yet unanalyzed. Brobeck (23) found that hypothalamic lesions in cats predisposed to insulin shock and to severe hypoglycemia, but that spinal cats recovered from a similar dose and that interruption of the hypophyseal stalk produced no insulin hypersensitivity.

Stimulation of the preoptic region of cats (24) produced a slowing of the heart rate, and a blanching with occasional inhibition of motility of the gastrointestinal tract (25), followed by a marked excitatory response. The onset of the inhibition was gradual; it lasted for several minutes and was not abolished by section of both vagi. Stimulation of the hypothalamus (24) for thirty seconds caused a sustained acceleration of the heart while stimulation of the infundibulum (25) raised the tone of the intestine and colon, accompanied by increased movement which endured at least as long as the period of stimulation. These responses of the intestine were found in spinal cats but were abolished by bilateral section of the vagus.

Without stating the exact position of the stimulating electrode in the hypothalamus, Weinstein & Bender (26) elicited dilatation of the monkey's pupil which persisted after section of the third nerve but was not obtained after cutting the cervical sympathetic trunk. Throughout the hypothalamus of cats electrical stimulation in the hands of Carlson, Gellhorn & Darrow (27) produced excitatory effects upon the sympathetic and inhibitory effects upon the parasympathetic; and, in those of Masserman (28), somatic manifestations of rage as well as autonomic effects such as hyperpnea, salivation, mydriasis, and piloerection. Masserman with Haertig (29) made three types of lesions in this region in cats. Lesions in the preoptic area made the cats either affectionate or



aggressive; those in the caudal hypothalamus gave the cats catalepsy, "muscular hyperreflexia," and an eleven-day fever with occasional poikilothermia; while those which were made between the optic chiasma and the corpus mamillare were frequently followed by an increasing malaise, rising temperature, and bronchopneumonia.

A different procedure was followed by Hemingway, Rasmussen, Wikoff & Rasmussen (30). Gold-foil electrodes were buried either in the anterior hypothalamus or in the posterior hypothalamus of dogs via a subtemporal approach. After a period of three months (for healing) the electrodes were heated. Heating the anteriorly placed electrode was followed by inhibition of shivering and vasodilatation; heating the posterior electrode, by sleep and a slight decrease in the intensity of shivering. Comparing the amount of heat necessary to apply to the surface of the animal with that necessary to give the hypothalamus, either to arrest shivering or to cause peripheral vasodilatation, these investigators reported respectively such figures as 2.26 kcal. and 0.013 kcal., 9.0 kcal. and 0.032 kcal., or ratios of surface heating to hypothalamic heating as 174 to 1 to arrest shivering and 281 to 1 to cause peripheral vasodilatation.

In spite of an intact heat regulatory center, cats with transection of the lower cervical cord (31) were unable to make the necessary adjustments for maintaining a normal body temperature if that of the environment dropped quickly and appreciably. If the drop were gradual, however, a fair degree of adjustment was made. Even this ability was lost after the cats were kept for long periods in a warm room. It is just possible that the hypothalamus exercises this control of body temperature by an efferent pathway. Certainly, this investigator with Wang (32) has been able to allocate the autonomic pathways of the bladder from the hypothalamus to the lateral funiculus of the spinal cord and to determine that its decussation was limited to the brain stem and the lower sacral cord.

The nucleus preopticus is composed of cells which appear to be a cross between nerve cells and glands cells. Scharrer (33) found these nerve-gland cells frequently multinucleated and the arrangement of their included chromatin and nucleoli to have every appearance of nerve cells. But their cytoplasmic inclusions seemed to pass through distinct phases similar to those observed



in gland cells. Similar nerve-gland cells were found in the head ganglia of cockroaches and in the cerebral organ of nemerteans (34). Examination of several related groups of the latter showed that the cells were epithelial and secondarily included within the neuraxis. Since these peculiar glandlike nerve cells, which characterize the nucleus preopticus in vertebrates, are found in the region of late closure of the central nervous system (because the anterior neuropore closes last along the lamina terminalis), it is not impossible that the closure may include cells of the ectoderm which are not true neuroblasts.

*The corpus striatum.*—The persistent attempts to analyze the function of the basal ganglia in animals have been meagerly rewarded. Liddell & Phillips (35) found no evidence of localization of function as sequelae to lesions in nuclei as separate as the claustrum, caudate, or lentiform. Rather, a persistent hypertonia of contralateral extensor muscles and of ipsilateral flexor muscles was so great that 2.5 to 3.0 kg. was necessary to flex the extremity in extension and 2.0 to 2.5 kg. to extend it in flexion. On the contralateral side the flexor reflex was delayed, the placing reactions and the closure of the eyelid were defective—a peculiar association of functional losses. The foot followed the palm of the observer's hand in halting fashion until the limb was fully extended, and at the moment of lowering a great extension at all joints was seen. If the lesion were unilateral, the cat circled to the side of lesion; if bilateral, the gait was stiff, and was performed "in a stealthy crouching fashion."

If the caudate nucleus in cats (under sodium pentobarbital anesthesia) was stimulated stereotactically, spontaneous movements of the ipsilateral limbs were "held" or inhibited, reflex activity of the lateral hamstrings was decreased, tone of the bladder and of skeletal muscle was inhibited, sweating was reduced, and the respiratory rate was depressed. The inhibition of tone in skeletal muscle is the only part of this picture of stimulation of one of the basal ganglia which resembled the function assigned by the lesions of Liddell & Phillips. From these results of stimulation of the caudate nucleus Freeman & Krasno (36) concluded that they had elicited a "conditioning" phenomenon—a tonic extrapyramidal "set" of the motor neurons of the final common path with reference to phasic activity of the corticospinal system.

The results as outlined for animals in these two papers ap-



proached, more closely than is generally the case, a part of the picture of basal ganglion disease in man. But some divergence here between the results of lesion of the basal ganglia in animals and man may always exist, for the peculiarities of motor patterning in man subsequent to injury of the basal ganglia may be due in large part to unconscious factors in the expression of his own individual character trend (37).

Papez & Stotler (38) have reinvestigated the fiber connections of the striatum in humans. They believe that the globus pallidus (not the caudate as previously given) receives fibers from the medial thalamic nucleus and sends out fibers to the ventrolateral thalamic nucleus via the fasciculus thalamicus and to the red nucleus via the offshoots from the ansa lenticularis and the fasciculus lenticularis. In the macaque Vidal (39) has found the medial division of the globus pallidus to be the origin of the pallidohypothalamic tract or Meynert's X bundle.

#### THE SUPRASEGMENTAL MANTLES

*The cerebellum.*—The Larsell-Dow division of the cerebellum into flocculonodular lobe and corpus cerebelli has proved useful to both experimental and clinical neurologists. Nevertheless, retention of the older divisions of anterior and middle lobes seems necessary if the corpus cerebelli is to be analyzed.

The axons of the Purkinje cells of the flocculonodular lobe terminated about the cells of the nucleus fastigii and the lateral vestibular nucleus, and those of the paraflocculus, about the cells of the nucleus dentatus. But the cortical projections of the whole part of the vermis of the rabbit, cat, and monkey, from the anterior lobe back to the uvula, was found by Jansen & Brodal (40) to end in the nucleus fastigii and the vestibular nuclei of the medulla oblongata, particularly, Deiters' nucleus. But the lateral part of the anterior lobe in the rabbit and cat projected upon the nucleus interpositus (the equivalent of the nuclei emboliformis et globus in man). More laterally, however, in the anterior lobe of the monkey the axons of the Purkinje cells terminated within the nucleus dentatus. In the monkey the lateral part of the lobus ansiformis (lateral part of Ingvar's middle lobe) projected upon the nucleus dentatus, and the more medial part, upon the nucleus interpositus. The paramedianus in all three forms studied sent its fibers also to that nucleus.

These writers conclude that the lateral part of the anterior



lobe may be wanting in the cat and rabbit. In other words, in the monkey the anterior lobe via the nucleus dentatus would be capable of activating a part of the central nervous system which that of the rabbit and cat could not.

This existence of a definite corticonuclear localization presupposes a similar distinct topographical correlation between cerebellar nuclei and those parts of the central nervous system to which the axons of these nuclei are distributed. Two types of anatomical localization must exist side by side in the cerebellum: (i) the spinocerebellar and the vestibulocerebellar, which Larsell and Dow have so beautifully outlined but which was described by Ingvar more than twenty years ago; and (ii) a corticonuclear, which in its greater detail is the contribution of these investigators. Interdigitating with these is that of the olivocerebellar relations.

The extensor tonus produced by ablation either of the anterior lobe of the cerebellum or of both pericruciate areas of the cerebral cortex in carnivores was summated by their simultaneous removal (41), producing an animal in which extensors, flexors, abductors, and adductors contributed to make a pillar-like rigidity of all four extremities. Not only were all four legs rigidly extended, but the head was retracted, the back arched, and the tail elevated. All stretch reflexes were markedly enhanced.

The results of cutting the anterior cerebellar peduncle by Fulton and his collaborators can now be compared to those which follow cutting both middle brachii. Much to the reviewer's surprise, Turner & German (42) found no change in the execution of learned behavior patterns. Evidence of retention of these patterns was to have been expected. Although they concluded that the cortico-ponto-cerebellar system was not necessary for precise manual functions or learned behavior, nevertheless, the perfection of the hand-eye coordination test was reduced by 20 to 30 per cent. A progressive incoordination between upper and lower extremities in locomotion and a disequilibrium were reported together with a decrement in spontaneous activity and a sluggishness of behavior, which increased with time, as the sequelae to bilateral section of the brachium pontis. This is the only study known to the writer in which sluggishness increasing with time was related to the lesion, as such.

These investigators have a unique opportunity to settle once and for all the morphological type of ending of the pons fibers, and



at the same time to look for a nonmedullated recurrent fiber (Ramon y Cajal's were medullated) which Chang (43) has described (in the monkey) for the first time. These recurrent fibers ascend almost to the surface of the cortex cerebelli then descend abruptly, forming narrow loops. It is possible that this fiber is peculiar to the primates for it is hard to believe that von K  lliker, Cajal, or van Gehuchten could have overlooked such a terminal in the cerebellum of the forms which they studied.

*The cortex cerebralis.*—Very few regions of the cerebral cortex have escaped some type of investigation during the year covered by this review. These investigations will be classified according to the major subdivisions of the cerebral mantle. Papers which deal with the subcortical centers for sight and for hearing will be discussed with their respective cortical projection areas.

No startling improvement in method of study of the cerebral cortex has been reported. Rather, the older methods of electrical stimulation and of ablation have been improved or combined with that of electrocorticograms. The cooperative use of anatomical, physiological, and electrical methods continues to prove productive.

*The frontal lobe: the precentral gyrus.*—A real contribution to topographical localization in man's precentral gyrus was made by Scarff (44) in the demonstration that the arm centers extend to the crest and that the leg centers are located entirely on the medial surface. Scarff has taken great pains to collect the literature on the electrical stimulation of man's precentral region. Foerster's last account (44a) placed the points for the trunk at the crest, the leg centers almost entirely on the medial surface.

The concentration of the leg area in man on the paracentral lobule is a definite contrast to the double representation of certain movements of the lower extremity on the medial and lateral surfaces which characterizes the chimpanzee's motor cortex (45). These electrical explorations of the precentral gyrus of the chimpanzee suggested the existence of several types of corticofugal systems because the movements elicited could be classified as activation (i) not only of discrete motor nuclei of cranial and spinal nerves but also of subdivisions of these nuclei, (ii) of spinal mechanisms which innervate extensor or flexor sheets of skeletal muscles, (iii) of brain stem integration systems, and (iv) of coinnervations of motor nuclear groups, which produced use



patterns characteristic of the chimpanzee. The most frequently elicited movements were flexion of the lateral four digits and adduction of the first. Isolated movements of the second or fifth fingers were rare; those of the third and fourth fingers, like the results of Sherrington's classical stimulations, did not occur. Different loci for antagonistic movements at the joints were obtained. Unlike Sherrington's results, vocalization, a light whistle, and salivation were produced in the animal. The liminal strength of the stimulating frequency for the arm and leg areas (area 4), 0.22 to 2.0 ma., was higher than for the face area (area 6), where it was 0.2 to 1.5 ma. The optimum frequency was 90 c. p. s.

Hines & Boynton (46) stimulated the precentral gyri of monkeys ranging in age from sixty-six days of gestation to one year after birth with the 60 c. p. s. sine wave current. Two types of movements were elicited—movements which could be allocated to the pyramidal unit (idiokinetic) and those which could not (holokinetic). Other phenomena produced by electrical stimulation were relaxation of tone, tonic innervation, fixation, and changes in respiration. Holokinetic movements were obtained in the youngest fetuses. The first idiokinetic movements appeared in the older fetuses (135 to 162 days of gestation). In these fetuses the idiokinetic points were isolated in three islands on the posterior division of the precentral gyrus by silent points, holokinetic points, or by those which gave relaxation of tone. When the monkey was between one week and four or five months of age, these idiokinetic islands were gradually eliminated by the encroachment of idiokinetic points upon the silent and nonidiokinetic points which were found upon the interregional borders of the leg, the arm, and the face areas, until all nonidiokinetic points tended to be localized on the rostral border of the precentral gyrus or on the paracentral lobule. The results of this study suggested that as the motor performance of the infant monkey proceeded from stage to stage, each part of that performance could be modified by the activity of the precentral gyrus; for at the time in which that performance was characteristic of the animal's motor patterns some part of those patterns were elicited by stimulation of this gyrus. For example, parts of the nursing pattern were produced from the face area, and parts of the infantile defecation pattern were initiated by stimulation of the leg area. The total contribution of the precentral gyrus to the



motor activity of the growing monkey cannot be read in the maturation of a single corticofugal projection unit. Rather, this gyrus seems to be, at each stage in the maturation of the animal, the cortical space through which the characteristic motor activities of the monkey can be initiated and modified.

Dusser de Barenne *et al.* (47) stimulated the cortex cerebri of young chimpanzees under dial anesthesia with pulses at frequencies varying from 1 to 40 per sec. They obtained the lowest thresholds on the posterior part of the precentral gyrus (band V) and on the anterior part of the postcentral gyrus (band VI). No motor activity was elicited by stimulation of their four suppressor bands even with four times the voltage used for the motor bands. However, suppressor bands I, III, and VII yielded relaxation of existing muscular contraction or a suppression of motor response or of afterdischarge of the motor bands. From the anterior part of the inferior parietal lobule they elicited facilitation when muscular tension already existed. In a similar study (48) on the macaque, suppression of motor activity obtained by the stimulation of area 4 was produced by the stimulation of the anterior border of area 4 (4S), of the postcentral gyrus, of area 8, and of area 19. This suppression travelled via corticofugal systems to some region in the tegmentum of the midbrain or medulla because it was found that neither the corpus striatum, the thalamus, the substantia nigra, nor the cerebellum were necessary.

Using implanted electrodes (without anesthesia), Clark & Ward (49) found that the response to cortical stimulation varied quantitatively with the duration and strength of the stimulus. When the duration of the stimulus was continued beyond the time of the response, epileptic seizures resulted, and the duration of such afterdischarges was predictable when the factors of variation were properly evaluated. In other words, the cortical point was stable when the conditions of its stimulation were stabilized [as was also found by Hines & Boynton (46)]. With Dribben these investigators (50) explored the motor cortex of normal and of "nervous" goats (a strain of goats in which myotonia is inherited) by stimulation with the 60 c. p. s. sine wave current. Whether the stimulus was applied under anesthesia in the usual way or without anesthesia (by means of implanted electrodes) no difference in the responses or in the strength of the stimulus necessary to evoke them was found between the two groups of goats. How-



ever, in the nervous goats weak stimuli produced quick movements free from myotonia, but intense stimuli elicited movements which at their onset gave evidence of myotonia, which in turn slowly gave way to clonic movements.

Bromiley & Brooks (51) and Brooks & Woolsey (52) have discovered the hind leg area in the opossum and in the rabbit, respectively, by electrical stimulation (60 c. p. s. sine wave) of the motor cortex. Removal of the area, which yielded movement of the hind leg, abolished placing with the contralateral leg and rendered hopping defective in the opossum, and in the rabbit caused a deficiency in hopping and placing with both contralateral limbs. Section of one pyramid in the rabbit produced deficiencies similar to that of ablation of foreleg and hind leg areas. But in the rabbit the region from which movements of the hind leg were elicited was not Brodmann's area 4. The pyramids of the rabbit seem to contain axons of cells other than those of Betz in the Vth layer of area 4.

Murphy & Dusser de Barenne (53) destroyed the upper five layers of a part of the arm area in the macaque and reported that "no observable difference" was found between the normal arm and the arm contralateral to the lesion at the end of two months. Either the area removed was not large enough to produce permanent loss, or the methods of examination were not sensitive enough to detect it, or the corticofugal systems from layer VI were able to initiate discrete movements and to inhibit an increase of tone. The electrocorticogram taken from the remaining VIth layer was reduced in both frequency and amplitude. It is to be regretted that the exposed VIth layer was not stimulated electrically.

Mettler & Mettler (54) have been studying the effect of acute lesion and of simultaneous stimulation of various structures in the nervous system upon phasic movements produced by electrical stimulation of the motor cortex in the cat. Phasic movements so produced were converted into tonic movements by cutting the dorsal roots, but they were not eliminated by ablation of part or of all the cerebellum or by transection of all the medulla except the pyramids. On the other hand, the cortex cerebri retained its capacity for spinal inhibition and for the production of epileptiform seizures after the corresponding pyramid was cut.

For several years Kennard (55) has watched infant monkeys and chimpanzees grow up after ablation of all of or parts of the



area frontalis granularis, and now she is able to compare those observations with studies on the deficient human infant. In the young of each of these species motor deficit appeared at the time skilled, coordinated movements normally developed, while spasticity was delayed. In these primates the paralysis and to a greater extent the spasticity were less severe if the causative lesion occurred in infancy. In the monkey, Kennard believed that this approximation was due in part to a reorganization of cortical function, because other motor deficits can be added by subsequent removals of the postcentral gyrus or frontal association areas.

*The frontal lobe and related areas.*—To a comparative neurologist the allocation of changes in emotion to the smell brain is unbelievable. And yet there it is. On the other hand, the least common denominator of the secondary olfactory center, the thalamic, striatal, and cortical centers for smell, are shared by all vertebrates. The decrease in the use of smell as an orientation sensibility in primates, particularly man, has not been accompanied by a decrease in the complexity of these nervous centers. In man the primary olfactory and accessory olfactory formations are differentiated at 8.5 weeks (crown-rump length of 26 mm.). Three weeks later the accessory olfactory formation has begun to regress, more rapidly on the right than on the left, a peculiarity also shared by Jacobsen's organ. Consequently, as humans we share with other mammals a period during development in which Jacobsen's organ and its primary receptive center are important (56).

The olfactory system has two cortical areas, a lateral or pyriform lobe, known in man as the uncus, and a medial, known as the hippocampus. Both the uncus and the hippocampus are related to nearby cortical regions and discharge their efferent systems into the epithalamus and the hypothalamus. The lateral olfactory cortex is closely related to a striatal nucleus, the amygdala. This nucleus is a complex of several nuclei. In man according to Crosby and Humphrey (57), the basolateral group of three nuclei and the "cortical" nuclei are more developed than in the subprimates studied. But the anterior amygdaloid area resembles that of the cat and the rabbit, and the lateral olfactory area, that of the bat.

Now removal of the olfactory bulb and stalk in cats (i.e., removal of the primary receptive areas for smell) was not followed by rage (58), nor was ablation of the frontal lobe unless the



extirpation encroached upon the tuberculum olfactorium. But injury to the tuberculum olfactorium itself, to the hippocampus-fornix system, particularly when the septum pellucidum was involved, and to the amygdaloid nuclei produced rage reactions. Superficial lesions of the pyriform lobe, however, were followed by slight and transitory symptoms of rage. Is it possible that Bard's "sham" rage should be allocated to loss of archipallial or paleopallial projections upon hypothalamic regions?

And certainly as in the cats of Spiegel and collaborators, removal of the prefrontal areas of man or isolating them from lower centers was not succeeded by rage reactions. Indeed just the opposite was the case. Mixer, Tillotson & Wies (59) tried Freeman's frontal lobotomy on two patients with agitated depressions. There was no change in the depression; rather, a loss of spontaneity, initiative, and interest, as well as a deficient thoughtfulness about the future (not always produced by cutting a few fiber tracts). On the other hand, bilateral removal of Brodmann's area 10 in a chronic epileptic was not followed by any positive neurological signs; the patient was easier to control, for he was no longer stubborn and unmanageable.

A similar result in a far more normal young man followed removal of less than one third of both frontal lobes (60). Fifteen months after ablation only two epileptic seizures had occurred. In spite of careful study of this patient no clinical or psychometric evidence of deterioration has been uncovered. The patient has worked half time on his father's farm, and his parents find him agreeable and easy to manage. But as the writers suggest, this patient has not been adequately tested because he has not been required to earn his own living. For this docility is not always a prerequisite. Examination of the areas removed showed that only area 10 has been completely and bilaterally ablated.

Waller's (61) study of the thalamic projections to the cat's frontal lobe showed certain homologies with Walker's similar study in primates. The gyrus preceus, the area frontalis granularis in the cat, received the axons of cells in the medial thalamic nucleus. The ventroanterior thalamic nucleus projected upon the motor cortex about the cruciate sulcus. The remainder of the ventral thalamic nucleus, passing medially to laterally, was projected to the cortex about the coronal sulcus, passing anteriorly to posteriorly.



As a part of his program of the analysis of thalamocortical relations Walker (62) has studied the cytoarchitecture of the area frontalis granularis in *Macaca mulatta*. Unlike other students of the architectonics of this region in monkeys, Walker has found the largest area on the lateral surface of the prefrontal region to be area 46. Such a finding implies that Brodmann, who originally divided the cerebral cortex into areas and gave them numbers, has made a serious mistake in application of his own differentiations and definitions to a large area in the brain of a species of which he studied a frontal series. This finding makes a restudy of the prefrontal areas of monkeys imperative, for area 46 hitherto has been considered to be a region of very late phylogenetic appearance. This cannot be said about Walker's transfer of the more ventral part of area 8 to area 45, because the region is small in extent and therefore might have been missed in certain orientations. Walker also found area 8 (called 8B) to extend over the crest of the lateral surface onto the medial surface to the sulcus cingulus. For this I thank him.

Lesions on the medial surface of the frontal lobe involving the corpus callosum have been described as producing apraxia. However, as far as the writer knows, no case of apraxia has been ascribed to lesion of the corpus callosum alone. Moreover, congenital absence of this neopallial commissure has been reported without record of abnormal neurological signs or of psychiatric states. So the part played by this giant commissure has been a mooted question. Certainly it is now known that the nerve fibers which compose it are not simple area-to-area correlation fibers (63). Nevertheless, division of this commissure in monkeys has been described as producing a definite syndrome. Yet when Van Wagenen & Herren (64) divided the corpus callosum in man (completely except for the posterior two thirds of the splenium) in an attempt to limit the spread of epileptiform convulsions, no apraxia followed, nor any change in mental status, nor in speech. And in six cases in which Van Wagenen completely divided the neopallial commissure, Akelaitis (65) found no disturbance of vision, either in recognition of objects or in determination of their size and color. There was no change in stereoscopic vision, and reading was unaffected. Further, Van Wagenen & Herren were unable to discover any change in athetoid movements already present, or in the previous condition of the reflexes examined.



Spasticity present before the operation was somewhat decreased afterward. Although no changes in associated movements of the hand were observed, those of the toes on the affected side which had accompanied movements of the toes on the normal side were lost. The convulsions were prevented from recurring if the greater part of this commissure was severed, unless the epileptiform centers were multiple. In other words, cutting the corpus callosum produced no new abnormal neurological signs, rather its effects although slight abated abnormal signs already present.

Would the sequel to cutting the corpus callosum in normal man have resembled that described for the monkey? Or is man not a monkey?

*The somesthetic cortex.*—At one time the region within the cortical mantle to which body sensibility is projected was known as the sensory cortex. And new knowledge of this cortex was dependent upon chance lesions within some part of the somesthetic pathways. Now three types of investigation enlarge our understanding of this general problem. The cortical projection of thalamic nuclei of primates and subprimates has been described with satisfactory simplicity if one investigator is read, but with bewildering confusion if the attempt is made to homologize the results of two investigators. The outline of the "sensory" cortex obtained by strychninization has transgressed upon the total breadth of the "motor" fields, far beyond the borders of cortical areas which receive thalamofugal fibers from nuclei in which the somesthetic lemniscus system terminate. Cortical and subcortical potentials, initiated by stimulation either of peripheral end organs in the natural manner or of peripheral nerves by electric currents, have been utilized in these studies.

In cats under pentobarbital anesthesia measurable electric reactions evoked by a tactile stimulus were picked up in the tegmentum, in the thalamus, in the internal capsule, and upon the cortex cerebri. Marshall (66) interprets as a quantum of activity the evoked repetitive discharge of (4 to 5 spikes in 6 to 8 sec.) a single thalamic neuron which has received a sustained lemniscus bombardment during that interval or longer.

Instead of using a tactile stimulus, Dempsey, Morison & Morison (67) stimulated the sciatic nerve of cats under deep pentobarbital anesthesia and recorded cortical potentials, finding a primary response (latent period, 8 to 10 msec.), a secondary



response (latent period, 30 to 80 msec.), and an inhibition of spontaneous cortical activity. The primary response could be interpreted as that of somesthetic pathways because destructive lesions of the thalamus and division of the medial lemniscus abolish it. The secondary response was both crossed and uncrossed below and above the anterior corpus quadrigeminum. The upper crossed component was found in the corpus callosum, and the upper uncrossed was abolished by lesions in the subthalamus. Symmetrical lesions of the lateral part of the midbrain destroyed both of these responses, but the inhibition of cortical activity remained. In a second communication (68) these investigators reported that a cortical response similar in latency to the primary was evoked when any part of the medial lemniscus-thalamo-cortical projection system was discretely stimulated. A generalized response, identical in wave form with the secondary and with medium latency, was obtained in all regions of the cortex by stimulation of as greatly separated nuclei as the nucleus amygdala, the subthalamus, and the nucleus subparafascicularis. Inhibition of spontaneous cortical activity was produced by stimulation of the cortical radiations, the internal capsule, and nucleus caudatus. Besides these, a generalized response of long latency (100 to 250 msec.) was evoked by stimulation of the fornix, corpus callosum, and radiations to the gyri cingulus et suprasylvius. In addition, a fast response, similar to spontaneous bursts of activity in the cortex of animals under anesthesia, was effected by stimulation of the anterior nucleus of the thalamus, the thalamic radiations, and the internal capsule. All of these responses except the primary suggest neuron connections between thalamus and cortex and striatum and cortex of which the neuroanatomist has no definite knowledge.

Dusser de Barenne & McCulloch (69) found that the structures necessary for the spontaneous electrical activity of the cerebral cortex were (i) the thalamic nucleus with which the area tested is connected and (ii) the deep layers of the cortex itself. What are the three outer layers of the cortex doing? Are they active only when peripheral end organs are definitely stimulated? Was the slow phylogenetic elaboration of the supragranular layers made for the reception of discrete stimuli only?

Marshall, Woolsey & Bard (70) studied the spatial distribution of cortical activity produced by stimulation of single points on



the skin. Tactile stimulation was delivered to hair covered areas by a small camel's hair brush and to the bare skin by the tip of a cat's vibrissa. The stimuli evoked discrete, surface positive potential waves in specific places on the contralateral cortex of the cat and monkey. In the cat a weak tactile stimulus applied to the dorsum of the forepaw produced separate maximal primary responses in three discrete cortical areas: (i) at the rostral tip of the lateral fissure, (ii) at the lateral tip of the cruciate sulcus, and (iii) at the lateral tip of the sulcus suprasylvius anterior. In the monkey a tactile stimulus on any part of the body always evoked within the cortical representation of that part primary responses on two or more areas. The response of shortest latency was found in Brodmann's area 3; that of longer latency, in area 2; and frequently another maximal response was discovered on or in the neighborhood of area 1. The spot of primary response was surrounded by submaximal responses such that the cortical overlap of submaximal responses for peripheral adjacent regions was reciprocal. These findings make a simple punctate somatotopical projection of skin areas upon the sensory cortex untenable. Rather, the localization of the maximal and submaximal responses on the cortical surface evoked by point stimulation in the periphery showed a definite stability and suggested the existence of a degree of separate thalamic projection upon the postcentral gyrus.

The primary response was present both in animals anesthetized with ether, pentobarbital, dial, or chloralosan and in unanesthetized animals. In the unanesthetized animal the primary response had a shorter recovery, longer-lasting facilitation effects, and a greater complexity of secondary reactions than in the anesthetized animal.

The sensory cortex of the chimpanzee as outlined by strychninization of the surface (71) extended from a line which cut across the posterior third of the fissura interparietalis to another line which cut transversely the anterior limb of the fissura frontalis superior. Within this area nine transverse strips were identified by their characteristics of either suppressing or firing activity in other parts of this broad reach of cortical surface. Four suppressor bands were found, one anterior (I) and one posterior (XI) to the "sensory" cortex, one anterior to the fissura precentralis inferior (III), and one on the postcentral gyrus anterior to the postcentral fissure (VII). The first two suppressed electrical activity in the greater part of the hemisphere tested.



The most extensive firing bands were II and VI, probably area 6 and area 3, respectively. The precentral gyrus itself was cut transversely into band IV, which fires both anteriorly and posteriorly, and band V, which fires only posteriorly. Band VIII, posterior to the postcentral fissure, fired the precentral (V) and the postcentral (VI) gyri and band X. Bands IX, IV, VI, and X fired two of the four suppressors, III and XI.

Similarly, in the cortex of the macaque (72) four transverse suppressor strips were found—in area 8, in the anterior border of area 4, in area 2, and in area 19—of which the first three were found with strychninization to fire into the nucleus caudatus.

The application of strychnine to the central nervous system has been used by Dusser de Barenne and his co-workers as a method for the study of the location and functional organization of sensory systems on the assumption that firing does not take place beyond the first synapse. At some future date this supposition must be tested by degeneration experiments. If one area "fires" another or "suppresses" another because the cell body lies in the firer or the suppressor band and its axon terminates in the fired or suppressed band, how shall the two "dud" areas in the chimpanzee cortex be interpreted, as areas having no inter-regional connections or as areas projecting their effects outside the region studied? The posterior "dud" area coincided with Campbell's "audito-psychic" area, and the anterior one with the face area (area 6) on the precentral gyrus.

Gerstmann (73) has described a syndrome of finger agnosia following lesions in the lower parietal lobule of man (a region which might be homologous to the posterior "dud" area of the chimpanzee), in which the patient has a disturbance of right and left body orientation. Knowledge of the middle three fingers was grossly disturbed; this was accompanied by difficulty in writing and in performing calculations. It is significant that calculation, which primitively is counting, should be associated in the cortex cerebri with a knowledge of the fingers.

*Optic pathways and the occipital cortex.*—The results of this year's investigations upon the optic system indicate that there is no simple basic pattern which can be applied to a particular species without adequate investigation of that species by methods of degeneration. Neither Packer (74) nor Jefferson (75) were able to trace any optic tract fibers to the nucleus pretectalis nor to the large-celled nucleus of the optic tract. Jefferson did not consider



that he had demonstrated termination of optic tract fibers in the ventral nucleus of the lateral geniculate body or that there was any evidence of either an anterior or a posterior accessory tract in the ferret. On the other hand, Packer saw a well-defined degeneration from the opposite eye enter the ventral nucleus and pass into the two accessory tracts in the phalanger.

Moreover, Gillilan (76), who studied the connections of the posterior accessory optic tract in several mammals, reported this bundle of fibers to be present in three species of bats, in four species of rodents, in the American shrew, in the cat (in which it is unmyelinated), and in the macaque (in which it is thinly myelinated and unmyelinated). The anterior accessory tract was identified beyond doubt in chiropterans, insectivores, and rodents, but not either in carnivores or in primates. The posterior accessory tract (the tractus opticus basalis) was large and heavily medullated in animals in which nocturnal vision is important. Nevertheless, in others this tract could be traced to subthalamic and midbrain centers. In the larval form of *amblystoma* the first fibers to develop in the optic tract were relatively large axons. These originated from all parts of the retina, penetrated the deeper parts of the optic tectum, and forming the tractus accessorius posterior, terminated in the lateral tegmentum or in the nucleus ectomammillaris. The small axons increasing in number during metamorphosis originated in the ganglionic layer of the four retinal quadrants and terminated superficially in the optic tectum forming a pattern of regional projection of the retinal quadrants (77).

Without making this neat distinction of termination of large or small fibers within the anterior corpus quadrigeminum, Jefferson was able to trace degenerated optic tract fibers from the contralateral eye into layers II and III of the optic tectum (in the ferret), and Packer found only contralateral fibers of this tract to enter the stratum opticum and the stratum griseum superficiale. Does this double penetration of the optic tectum in mammals form the anatomical framework for a double function, as Herrick interprets this arrangement in *amblystoma*, or is this double penetration a phylogenetic remnant? It may be well to remind the reader that Brouwer found a beautiful regional projection of the contralateral eye in the anterior corpus quadrigeminum of the dog, slight indication of retinal localization in the optic tectum of the cat, and none whatever in the monkey.

But in the case of the dorsal nucleus of the lateral geniculate



body of the ferret Jefferson found a point-to-point representation of the retina similar to that reported by others for the cat and certain primates. Packer took his investigation a step further and described the ipsilateral fibers of the optic tract as terminating in the dorsal nucleus of the lateral geniculate body in three zones, 2, 4, and 5, and the contralateral fibers, in two zones, 1 and 3. In retrograde degeneration after removal of the area striata, the homolateral laminae 2 and 4 were more degenerated than lamina 5, and the heterolateral laminae 1 and 3 were also well degenerated. Such a finding suggested that axons of layer 5 might terminate in some other thalamic nucleus. The cortical projection of the dorsal nucleus resembled that described by Bodian for the American opossum. The corticofugal projections terminated in the stratum opticum of the superior colliculus and in the dorsal nucleus of the lateral geniculate body (a few only).

Neither Jefferson nor Packer found any retrograde degeneration in the ventral nucleus of the lateral geniculate body following removal of the area striata. Although Jefferson could not convince himself that any fibers of the optic tract terminated in this nucleus, he did describe two of the typical connections of this nucleus, namely, those with the zona incerta of the thalamus and with the anterior corpus quadrigeminum. In the cat O'Leary (78) described two types of nerve cells within the dorsal nucleus, principal cells and short axon cells. The axons of the former passed out via the optic radiations; those of the latter connected the three layers of the nucleus and ended upon the dendrites of the principal cells. The large myelinated fibers of the optic tract bifurcated but did not terminate within the ventral nucleus. Collaterals from one of these bifurcations ramified between the three layers of the dorsal nucleus and might thus reach the dendrites of the short axon cells. No single nerve fiber supplied terminals to the principal cells in more than one layer, and each principal cell made contact with several terminals of different optic tract fibers. The thinner optic tract fibers bifurcated dorsal to the ventral nucleus, sending terminals from that bifurcation to cells within that nucleus. The destination of the other branch of both the thicker and the thinner fibers was not determined. From this anatomical arrangement within the dorsal nucleus O'Leary concluded that little or no self-reactivation could occur within this nucleus and that the short axon cells formed a synchronizing mechanism.

Le Gros Clark (79) devascularized minute areas in the area



striata near the sulcus lunatus of the macaque and studied the extent of the Marchi deposit within the cortical layers and the site of retrograde degeneration within the dorsal nucleus of the lateral geniculate body. No Marchi deposit was found to extend further than 4 or 5 mm. from the site of the lesion. Retrograde degeneration in the homolateral dorsal nucleus of the lateral geniculate body after lesions of 1 sq. mm. within the area striata radiated into all six laminae of that nucleus. From these findings Le Gros Clark concluded that, contrary to the generally accepted opinion, association fibers were short (never longer than 5 mm.), and that the projection unit from dorsal nucleus to the area striata fanned out in radial fashion from cells within each of the laminae of that nucleus. But this author as well as others had previously found that the smallest lesion in the retina produced changes in a group of cells in all the corresponding layers (layers 1, 4, and 6 from the contralateral retina; layers 2, 3, and 5 from the ipsilateral retina) in such a manner that the receptive unit of the dorsal nucleus would be formed by a narrow band of cells radiating from the hilum, involving layers 1, 4, and 6 on the opposite side and layers 2, 3, and 5 on the same side. After section of the optic tract in this animal (80), each axis cylinder of this tract sprayed out into five or six branches, each of which terminated upon a single cell in the dorsal nucleus. This terminal was the only terminal shown to be present on any one individual nerve cell within this nucleus! These neat anatomical arrangements suggest that optic impulses arrive at points on the area striata from corresponding points on the retina of both eyes.

Each one of these studies emphasized anew not only the interdependence of dorsal nucleus and area striata but also the complete independence of the ventral nucleus and the corical projection area for sight. If, as Brouwer has maintained, no degenerating optic fibers can be traced into the pulvinar, and if, as all authors think, the lateral geniculate body is related to the pulvinar, and if the dorsal nucleus entertains only cortical relations, then the pulvinar would by exclusion receive its optic connections from the ventral nucleus of the lateral geniculate body, unless the fibers of the optic radiations bifurcate. But the writer has failed to find the pulvinar listed as one of the regions which receive axons from the ventral nucleus. In view of Jefferson's inability to satisfy himself that fibers of the optic tract terminate within the ventral nucleus



of the ferret, and of O'Leary's and of Packer's clear-cut anatomical demonstration of such terminals within that nucleus in the forms they studied and the uncertain status of the relation of these nuclei to the pulvinar, a reinvestigation of the connections of the ventral nucleus of the lateral geniculate body is indicated.

Moreover, in primates as high as the macaque Klüver (81) has produced good evidence that light impulses reach some part of the cortical mantle in the absence of both area striata. If so, then those impulses according to the data in hand would be obliged to attain the cortical level either via a thalamic connection with the ventral nucleus of the lateral geniculate body or via tectothalamic pathways, described at present only in lower mammals. Klüver removed both occipital lobes from two monkeys and trained them to obtain their food by pulling in a stimulus box distinguished by an attached light. Testing after twenty minutes of dark adaptation, he found that these two animals could respond differentially to situations involving (i) a sudden appearance of light, (ii) differences in lights continually present, and (iii) differences in position of lights, but that these differences were not in brightness of the object as such, but rather in the density of the luminous flux which entered the eye. In one animal he thought that the configuration of the light stimulus might be effective in determining which box was pulled in, but there was no evidence that color as such could be correctly utilized. It was rather the relative intensity of the light emitted by the color which determined the correct reaction. But when light on the boxes had to be distinguished in daylight conditions, correct responses were lost. For example, in the presence of .0004 millilamberts both monkeys reacted correctly to Wratten filter #74, in that of .067 millilamberts the response was disturbed, and in that of .91 millilamberts the response was abolished. In the case of black or white surfaces correct responses could be learned only under conditions of very low illumination.

Finley (82) found that the scores which rats attained in running an elevated maze fell into a normal distribution when the individual rats were classified according to their complete dependence upon or complete independence of visual stimuli. The interference in accuracy was no greater for enucleation of the eyes than for destruction of the area striata. Their scores made under either of these conditions showed no significant differences from



the number scored in the dark during the last preoperative runs. Lesions of the cortical mantle which involved similar extents of this mantle produced greater losses of accuracy if the area affected more than one functional region, than if a lesion of similar extent was limited to one functional region only. These findings negate any theory of equipotentiality of the cortex cerebri even in the rat!

The results of Walker & Weaver's (83) repetition of electrical stimulation of the occipital lobe of the monkey varied little from the reports of earlier workers. Conjugate deviation of the eyes to the opposite side and downward was obtained from the dorsal division of the area striata; conjugate deviation to the opposite side and upward, from the ventral division of this cortical region—in other words, movement of the eyes toward the field of vision represented in the cortical projection area for sight. Stimulation of six points on the medial surface, of which four were probably in area 18, gave simple conjugate deviation to the opposite side; and of three points on the lateral surface, anterior to the sulcus lunatus yielded some contraction of the extrinsic ocular muscles and respectively, constriction of the pupil, closure of the eyelids, and widening of the palpebral fissure.

The report by Halstead, Walker & Bucy (84) of two cases of unilateral removal of the occipital lobes focuses attention again upon the question of localization of "macular" vision. The largest removal was followed by sparing of central vision for brightness, for color, and for the discrimination of form. On the other hand, the smaller ablation, which did not include all of the area striata, caused a complete perpendicular splitting of central vision for color, for brightness, and for the discrimination of form. These two divergent results suggest an individual variation in the distribution of the axons of the ganglionic layer of the retina within the optic chiasma. At least in one case no collaterals from the optic radiations passed to the opposite occipital lobe via the corpus callosum. Nevertheless, the question of the anatomical arrangement of the axons forming the macular bundle can not be settled until a unique situation arises, namely, one which calls for unilateral removal of the occipital lobe, followed subsequently by the necessity to ablate the temporal lobe on the same side.

*The temporal lobe.*—No true koniocortex has been identified in the temporal lobe of carnivores. Location of the auditory projec-



tion area in the cerebral cortex of these animals was therefore dependent either upon mapping the region to which the medial geniculate body sent fibers or upon outlining the area in which surface-positive potentials were evoked by stimulation of the end organ of hearing. The cortical area for hearing in the cat was delimited by mapping such potentials evoked either by click stimulation of the spiral organ (of Corti) (85) or by electrical stimulation of cochlear fibers within the spiral osseous lamina (86).

With his technique Ades outlined the auditory cortex as an area bounded anteriorly, dorsally, and posteriorly by the whole of the ectosylvian sulcus and ventrally by the superior tip of the sulcus pseudosylvius—a region which corresponded to that which he found to receive the medial geniculocortical radiations. Woolsey & Walzl recovered the surface potentials evoked by stimulation of the cochlear fibers at four points in the basal turns, at one point each in the second and apical turns. The basal end of the cochlea projected to an area surrounding the superior end of the anterior ectosylvian sulcus, and the apical end, to a region just behind the superior limit of the posterior ectosylvian sulcus. Intermediate regions were represented in band-like zones between these two limits. Corresponding points of the two cochleae projected to the same cortical region of one hemisphere and gave rise to potentials of similar magnitudes and latencies. Some other difference between the impulses reaching the cortex from these two end organs must exist, for otherwise how is the localization of sound possible?

No differentiation of the medial geniculate body into nuclei distinguished respectively by cortical and by subcortical connections has been reported. Besides the cortical projection, Ades described diffuse connections with the central grey and midline nuclei of the thalamus, with the posterior commissure and the tectum in the midbrain, and with the deep portion of the anterior corpus quadrigeminum. Recurrent fibers were described as passing not only from the cortex to the medial geniculate body, but also from that body to the posterior corpus quadrigeminum via the inferior quadrigeminal brachium, and to the trapezoid body among the axons of the lateral lemniscus. Ades found no marked connection with any motor nucleus and thought that the commissure of Van Gudden had nothing to do with this particular thalamic nucleus.



## CONCLUSION

Although no new technique was used to investigate the central nervous system during the past year, long-held conceptions were disturbed. The area of synaptic surface on the nerve cell has been extended, the status of the typical ventral horn cell as always motor has been challenged, and nerve cells entertaining only one terminal have found. The cochlea was projected upon the cortical mantle, and the anterior cerebellar lobes developed a new function. The infant precentral gyrus partook in the patterns of activity at each stage of development, and the corpus striatum at last yielded some anticipated data.

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DEPARTMENT OF ANATOMY  
JOHNS HOPKINS UNIVERSITY  
BALTIMORE, MARYLAND



# THE AUTONOMIC NERVOUS SYSTEM<sup>1</sup>

BY KENDRICK HARE AND JOSEPH C. HINSEY

*Department of Anatomy, Cornell University Medical College,  
New York City, New York*

## INTRODUCTION

Three systems for describing the autonomic nervous system are in use. One, based upon the type of chemical transmitter, is useful only in reference to postganglionic neurons, which are designated as cholinergic or adrenergic. The other two are morphological and differ largely in that one recognizes an afferent as well as an efferent component of autonomic innervation. In this review, the most convenient and descriptive terminology will be used without any attempt to employ any one system exclusively. The greatest problem in preparation of this review has been, not systems of nomenclature, but a large and ill-defined zone which overlaps both neurophysiology and the pharmacology of the autonomic nervous system. Despite the fact that experiments with autonomic drugs continue to provide a great deal of information about the functions of the autonomic neuroeffectors, the space allotted permits the inclusion of only those which seem particularly germane to the immediate topic.

Reviews on related subjects which have appeared within the year include an historical one by Sheehan (1), one on the adrenal medulla by Cori & Welsh (2), one on vascular changes during inhalation anesthesia by Meek (3), and one by Schmidt (4) on the carotid and aortic bodies. From the long list of articles submitted by associates and former students as a tribute to Hess, those relating to the autonomic nervous system have been selected for this bibliography (5 to 17).

## ANATOMY AND EMBRYOLOGY

*Embryology.*—The experiments of Jones (18) are intended to settle the question of the origin of sympathetic ganglion cells. He concludes that they come from the ventral part of the neural tube. Mihálik (19), from observation of silver-stained rabbit embryos, similarly concludes that the ganglia come from cells which develop

<sup>1</sup> This review covers the period up to August 25, 1941.



in the motor part of the medullary plate and emigrate from the spinal cord and medulla over the ventral roots. In a comparable manner, the cells of the ciliary ganglion are derived from the oculomotor nucleus, and arrive at their ultimate position by migrating along the developing oculomotor fibers. All postganglionic nerve cells come from the anlage which will later provide their preganglionic innervation.

Additional experiments by Jones (20) have shown that removal of the hindbrain of 48-hour chicks prevents the formation of neuroblasts in the heart, esophagus, and gizzard, even though the nodose ganglia and the vagi develop. Two conclusions can be drawn from this: the sympathetic ganglia do not contribute to the early plexus of the heart, esophagus, and gizzard; and the plexus has a different origin from that of the nodose ganglia. Becker & Windle (21) observed a vagal supply to the stomach in cat fetuses as early as 7 mm., when the sympathetic trunks were in a formative stage. Gastric motility was observed as early as the 16.5 mm. stage, and even then a sympathetic contribution to the stomach is questionable. Weber (22) has described the development of the gastroduodenal plexus in the chick embryo.

Sensory ganglion cells of the mixed cranial nerves are derived from the ectodermal placodes, according to van Campenhout (23). He apparently considers the placodes completely independent of any inductive action of the crest cells in the chick. This experimental work gives support to previous observations indicating the need for a revision of the generally accepted view that neural crest cells give rise to all of the sensory cranial ganglia, especially since Jones (20) has shown that extensive removal of the neural crests along the hindbrain and cervical cord does not prevent the formation of the nodose ganglia.

The development of the solitary tract, described from graded series of cat, rat, sheep, and human embryos, depends upon contributions from cranial nerves VII, IX, and X (24). There is a suggestion that the fifth nerve also adds fibers to the tract. Kimmel (25) observed fibers from cranial nerves VII, IX, and X in the solitary tract. While he considered the sensory ganglia of these nerves to be of neural crest origin, he noticed a thickening of the placodes associated with the ganglia.

*Chromaffin tissue and paraganglia.*—Hollinshead (26) has recently written a review of the literature on chromaffin tissue and



paraganglia in which he advocates an experimental analysis rather than a speculative attitude. In a more specific article (27), he arrays his experimental studies on the innervation and function of aggregates of epithelioid cells associated with the abdominal vagus, against the descriptive and imaginative writings of Goormaghtigh (28). Hollinshead found these masses of cells structurally identical with the chemoreceptors of the carotid body. Their abundant nerve supply is derived from spinal dorsal root ganglia, but reaches the abdomen by coursing along with the vagi and splanchnics. Experiments indicate that functionally these structures are chemoreceptors, and their stimulation causes respiratory responses. The supracardial bodies in the cat also seem to have a sensory innervation, derived in the greater part from the left vagus (29). Vagal section below the nodose ganglion causes a degeneration of the nerve supply of these bodies, but section above the nodose is without effect.

In preparations of newborn mice, stained according to Ranson's pyridine-silver technique, richly innervated little bodies along the renal veins have been seen by De Muylder (30). Without any experimental evidence, he thinks that these bodies may be chemoreceptors which reflexly regulate renal glomerular blood flow. In the human temporal bone small structures similar in appearance to the carotid body have been found along the tympanic ramus of cranial nerve IX; Guild (31) suggests the name "glomus jugularis" for these structures.

Celestino Da Costa (32) believes that all "paraganglia" are the same, and differ only in degree of development and differentiation. The advantages of this unitary concept are certainly not apparent.

In a cytological study of the adrenal medulla, the cells were found arranged as columnar epithelium around the veins (33). The venous face of the cell provides for the discharge of epinephrine; the opposite face of the cell, which receives the innervation, is in contact with an arterially supplied capillary. Stimulation of the splanchnic nerves causes a change in the secretory granules, an increase in the number of secreting cells, and a liberation of epinephrine into the veins. McFarland (34) has shown that the innervation (mainly preganglionic) of the adrenal medulla in the rat is derived from the lower thoracic segments, passes over the splanchnics to end in direct contact with the medullary cells. The



cortex is not innervated. The number of fascicles and the number of fibers decreased progressively from the cow to the rat.

In the human fetus, detectable amounts of epinephrine in the adrenals appeared by the third month, and in the paraganglia by the fifth month (35).

*Heart and blood vessels.*—In Part II of his studies on the innervation of the heart, Nonidez (36) first considers the aortic nerve. In addition to the large fibers with reticulated swellings in their plexiform terminations, there are fine fibers whose endings he thought were not merely pressoreceptors, but special ones that are "the last to cease functioning when the blood pressure reaches the 200 mm. Hg. level." The innervation of the arterial ligament, partly by postganglionic parasympathetics, provides anatomical explanation for the contractions of the ductus arteriosus on stimulation of the left vagus. The terminations in the superior and inferior vena cava persist after upper thoracic sympathectomy, a fact which indicates that they are of vagal origin. Their function, even if sensory, is not necessarily pressoreceptor, for it is just this region—that Ballin (37) stimulated by distension without obtaining any vasomotor responses. The nerve endings normally seen in the pulmonary veins were absent from three sympathectomized cats; therefore these fibers arrive at the heart by way of the sympathetic nerves. This is not considered proof of their thoracic origin, because they might be vagal fibers that have become mixed with the sympathetics through their multiple anastomoses. Pannier (38), in studies similar to those of Nonidez, describes sensory terminations in the superior vena cava, the pulmonary veins, and in the node of Keith and Flack of the adult cat's heart. In addition he found nerve endings in the atria which provide an anatomical basis for Jarisch's interpretation of his experiments on the veratrine effect. The afferent paths for impulses initiated in the atria by veratrine have been described by Jarisch & Richter (39). The innervation of the frog heart has been described (40, 41).

An extremely abundant innervation of the capillaries is seen in methylene blue preparations of the cat's bladder (42). Unmyelinated fibers, supplying the small blood vessels, degenerate almost completely after sympathectomies that probably left some postganglionic neurons intact. Myelinated fibers, which terminated on small blood vessels and also innervated fat cells along the course of the vessels, persisted after sympathectomy, but disappeared after section of the dorsal spinal roots.



*Iris.*—Anatomical studies by Langworthy, Ortega & Teitelbaum (43) on the rabbit's iris support the often repeated observation that pupillary dilation is effected through oculomotor inhibition. The sphincter is well developed, but only scattered muscle fibers appear to be dilators. There are so many fibers to the sphincter that every muscle cell might well receive direct innervation; no mention is made of nerves to the dilator muscles, and the authors seem to be toying with the idea that there are none.

*Digestive system.*—Alexander (44) has stained what appears to be an uninterrupted terminal plexus in the wall of the cat's gall bladder. Oleandrov (45), by adding various pharmacological agents to his staining solutions, imparts to them a special affinity for different kinds of nerves. He has used his method in studying the nerve supply of the pancreas. A neuroinsular complex has been found in the pancreas in a large number of species (46), and its reduction was associated with diabetes mellitus in five human cases.

*Pituitary.*—The pituitary has two distinct sources of nerve supply, the hypothalamus and the peripheral autonomic ganglia, which fortunately send their fibers into the gland by separate routes. Section of the pituitary stalk eliminates the first type, while the second might be only partially eliminated by removal of the superior cervical ganglia, if the sphenopalatine makes a contribution as suggested by Zacharias (47). Brooks & Gersh (48) eliminated most of the fibers to all parts of the pituitary by stalk section in the rabbit, while only a part of the nerve supply to the anterior lobe degenerated after superior cervical ganglionectomy. In the rat no detectable reduction of nerves in the anterior lobe followed the sympathectomy, but after stalk section no fibers were found distal to the lesion. Roussy & Mosinger (49) have also described the innervation of the pituitary.

*Testis.*—Terminations of nerve fibers about the Leydig cells of the testis in man have been described by Okkels & Sand (50).

*Cervical sympathetic.*—The complexity of the cervical sympathetic trunk has attracted considerable comment; the nerve contains vagal fibers in addition to pre- and postganglionic sympathetics. Anastomoses between the vagus and the cervical sympathetic have been found in the dog, cat, and rabbit (51). After section of the ventral roots of  $T_1$  to  $T_6$ , which caused degeneration of the preganglionic sympathetics, fascicles of fibers persisted in



the cervical sympathetic trunk and could be traced upward to join the vagus (52). Verdonk (53) apparently encountered this situation in tracing the afferent paths from the aortic and carotid bodies concerned in respiratory reflexes. In a study of the innervation of cerebral blood vessels in the cat, Koopmans (54) found that the two cervical sympathetic trunks often have a different composition. The right nerve contains only vasoconstrictors; the left contains vasodilators as well as vasoconstrictors in 70 per cent of the animals. This left trunk could be divided into two fascicles, the larger one containing the constrictor fibers, the finer one the vasodilators. Stimulation of this fascicle also caused a general fall in blood pressure. Foley (55), however, from fiber counts on the cervical sympathetic trunk after thoracic dorsal and ventral root section, and after superior cervical ganglionectomy, concluded that the trunk was composed only of ascending preganglionic and descending postganglionic fibers.

The distribution of the autonomic fibers in the head of *Rana pipiens* is described by Barnard (56).

#### EFFECTORS

*Smooth muscle.*—Bozler (57) has presented a convincing and well-supported analysis of the effects of epinephrine and sympathetic nerve impulses on smooth muscle. Both have an initial excitatory effect, but both diminish excitability as determined by response to electrical shocks. During this phase a complete block of muscular conduction may also develop. The diphasic mechanical response of smooth muscle is the result of these actions of epinephrine and sympathetic nerve impulses, for, as the excitability of the tissue is depressed, contraction is followed by inhibition. Either phase may be dominant. Bozler suggests that the great variability in the response of smooth muscle may be thus explained without assuming any change in nervous mechanism. For example, during estrus, the response of the cat's uterus to electrical shocks is conducted so that waves and rings of contraction are initiated. During anestrus, the muscular responses are local (58). Bozler (59, 60), using first a condenser-coupled and later a direct-coupled amplifier, concluded that slow potentials from smooth muscle are artifacts; but Balassa & Gurd (61), using a direct-coupled amplifier, have recorded slow rhythmic potential waves in the anestrus cat uterus. In addition, there are spike potentials during contraction which occur in the estrous



uterus or in late pregnancy. The significance of these potentials and their relationship to mechanical responses and conductivity in the uterus under various hormonal influences is far from clear. However, the greater conductivity from cell to cell in the estrous uterus is associated with strong, coördinated contractions (61, 62).

Agar (63), however, reports that epinephrine causes first an inhibition, then a delayed contraction of the physostigminized uterus of the immature guinea pig. A prostigmine-like substance, when substituted for physostigmine, also caused a delayed contraction in response to epinephrine. Since physostigmine and the prostigmine-like substance share the property of inhibiting cholinesterase, Agar feels that "this invites the hypothesis that the secondary epinephrine contraction is due to a release of acetylcholine." The use of drugs in analyzing the action of nerve impulses and "chemical transmitters" on effector tissues is at times extremely helpful. However, there has developed an unfounded faith in the specificity of action of some of these drugs, especially ergotoxine and atropine. The falsity of this faith has been emphasized by Hebb (64) in a report on the bronchomotor responses to stimulation of the stellate ganglion and to injection of acetylcholine. She says, "ergotoxine suppresses the acetylcholine bronchial response so that there are no longer grounds for assuming that ergotoxine acts specifically to prevent only adrenergic nerve motor responses. Nor can it be assumed that ergotoxine will not act to prevent the motor response to cholinergic nerve stimulation."

The effects of stimulating a single nerve fiber to the vascular bed of the retrolingual membrane in the frog vary, in some instances, with the intensity of the electrical stimulus (65, 66, 67). Excitation of several fibers in the same field may produce a response in the same limited vascular bed, a fact which suggests a smooth-muscle motor unit. Often the response was limited to a capillary. However, very few nerve fibers could be traced in methylene blue preparations to the terminations of the capillaries; most of the nerve plexus invested the arterioles and precapillaries. This complex nerve network appears anatomically continuous, but its division into functionally discrete units was demonstrated by the excitation experiments. Langworthy & Hesser (42) found enormous numbers of nerve fibers to the capillaries in the cat's bladder, and were able to establish that they were postganglionic sympathetics, since they disappeared after excision of the lumbosacral sympathetic



chain. Capillary contractions, under the control of sympathetic nerve fibers, have been observed in a chamber in a rabbit's ear (68).

Sympathetic nerve stimulation causes a greater vasoconstrictor response in the rabbit's ear when the calcium concentration of the perfusing fluid is increased, while the response to injected epinephrine is diminished (69). This is confirmation of the observation by Earley (70) that the injection of calcium augments the pressor response to excitation of the thoracic sympathetic chain. Calcium appears, therefore, to facilitate the liberation of an epinephrine-like substance at the nerve endings, since it does not augment, but depresses the response to epinephrine. Potassium has an opposite effect, especially on the response to nervous stimulation. Dawes (71) studied its action on blood vessels, particularly those of contracting muscle, and his findings led to the suggestion that the vasodilatation which occurs there may be due to the release of potassium ions. The effectiveness of drugs, particularly "chemical transmitters," on nerve-free smooth muscle has again been demonstrated; in this case the muscle used was that in the chick amnion (72).

*Cardiac muscle.*—Studies on the effects of epinephrine and acetylcholine on cardiac muscle extend from annelids to man, but no attempt will be made to present them on a phylogenetic basis. Garrey (73) localizes the effect of acetylcholine on the limulus heart to the cardiac ganglion, where its effectiveness was enormously increased by physostigmine. The myoneural junctions did not respond to acetylcholine even in the presence of physostigmine. Davenport (74) found that, while acetylcholine inhibited the molluscan heart, it stimulated the heart in arthropods. The latter observation has also been made by Welsh (75) who found that acetylcholine inhibited the pulsating blood vessels of annelids and the hearts of molluscs and vertebrates. Perfusion of the lobster heart with physostigmine reduced not only the excitatory, but also the toxic threshold to acetylcholine; both effects were attributed to inhibition of cholinesterase. Nervous inhibition of the decapod heart (76) is apparently not effected through a cholinergic mechanism; perfusion with physostigmine lessens the inhibitory response to nervous stimulation and atropine augments it.

A mixture of epinephrine and acetylcholine will initiate contractions in the chick embryo heart that has stopped beating, when neither drug alone is effective (77).



Cohn & Macleod (78), from records of the electrical activity and the internal pressure changes of the mammalian heart, concluded that the effect of acetylcholine was to diminish the force of contraction and the duration of the excited state. They were also able to conclude that acetylcholine acts on the vagus endings rather than on the muscle proper.

*Capillary permeability.*—The influence of the autonomic nerves is not limited to the contractile elements of the vascular system. Acute pulmonary edema is produced in vagotomized rabbits by the rapid intravenous infusion of normal saline solutions, while the same infusion has but slight effect on normal animals (79). The effect of vagotomy is immediate and cannot be duplicated by the injection of atropine. According to Engel (80), sympathetic activity increases capillary permeability while sympathectomy decreases it. He observed the transfer of dyes, administered intravenously, across the synovial membrane of the knees in dogs, cats, and rabbits after unilateral sympathectomy. His report agrees with the thesis of Freeman that shock is produced by prolonged overactivity of the sympathetic nervous system, or by long-continued injection of epinephrine (81). A large decrease in plasma volume regularly attends shock produced in this manner, and the necropsy findings indicate a generalized loss of fluid into the tissue spaces and lumen of the gut (82). Freedman & Kabat (83) seriously doubt that hyperactivity of the sympathetic system is responsible for shock induced by afferent impulses, even though it has been established that trauma to a limb connected to the body only by its nerves could cause shock (84). Moon (85) has criticized Freeman's theory even more severely.

*Glands.*—Sympathetic influence on gonadotropic activity of the pituitary is advocated by Friedgood (86, 87). His earlier experiments on the production of ovulation in the rabbit and cat by stimulation of the cervical sympathetic trunks have been extensively repeated in this laboratory without once causing ovulation (88). Friedgood & Bevin (86) report that removal of the superior cervical ganglia is effective in inducing pseudopregnancy in the rat, but the specificity of the operation is doubtful as Zacharias (47, 89) observed pseudopregnancy after removal of the sphenopalatine ganglia. Britt (90) has found that psychic stimuli cause an estrogenic response in rats which is abolished by sympathectomy.



Vitamin A is released from the liver by splanchnic nerve stimulation (91) and by the injection of epinephrine (91, 92) in a manner similar to the liberation of glucose or plasma proteins.

With the exception of the pars nervosa of the pituitary, glands are altered slightly, if at all, in histological appearance by denervation. Denervation of the monkey prostate appears to have no effect on its histological structure (93).

*Humoral transmission.*—Since Dale's early studies, the action of acetylcholine has been considered separable into muscarine- and nicotine-like categories. Atropine abolishes the muscarine-like effects, but has little influence on the nicotine-like actions. Abdon (94), impressed by the fact that much larger amounts of acetylcholine are required to produce nicotine-like than to produce muscarine-like effects, thoroughly investigated the relationship between the amount of acetylcholine required to produce a given response and the amount of atropine required to abolish it. His studies, embracing both muscarine- and nicotine-like effects, reveal a constant ratio between the activating concentration of acetylcholine and the inhibiting concentration of atropine. Therefore the quantitative differences between the two effects of acetylcholine in regard to atropine antagonism do not signify a fundamental difference in action. Abdon's interpretation is that of Clark (95) and of Gaddum (96) that atropine and acetylcholine compete for the same receptors; preliminary treatment with atropine fixes some of these receptors so that the sensitivity of the tissue to acetylcholine is diminished. Jang (97, 98) employs the same theory in explaining the antagonism of sympathicomimetic amines to epinephrine.

Potentialiation of acetylcholine responses by a large number of substances—fluorine, ergotamine, quinine, oxalate, citrate, strophanthin, and changes in pH—is not associated with a decrease in cholinesterase activity (94). Nor does denervation of muscle sensitize by diminishing cholinesterase activity (99). Abdon therefore assumes that potentiating agents act on the acetylcholine mechanism, rather than on the esterase system.

The action of physostigmine in potentiating responses to nerve impulses or acetylcholine is apparently related to the inhibition of cholinesterase, though any causal relationship is questioned by Meng (100). Nachmansohn & Meyerhof (101), from studies on the electric organ of torpedoes and rays, found a close parallelism



when the voltage and the number of plates per cm. were compared with the cholinesterase concentration. Boell & Nachmansohn (102) found the enzyme in much higher concentrations in the sheath of the giant fiber of the squid axon than in the axoplasm. This observation has suggested to Nachmansohn (103) that "acetylcholine does not act specifically as a 'synaptic transmitter' of nerve impulses to effector organs, but is intrinsically connected with electrical changes occurring everywhere at the surface of the neurons during activity." Lorente de Nó (104) has long suspected that it was not an intrinsic element in synaptic transmission, for he found the liberation of the acetylcholine-like substance was dissociated from synaptic activity in sympathetic ganglia. Runcan (105) observed a liberation of acetylcholine in the perfusion fluid of the isolated frog's heart in the absence of vagal stimulation. Bacq & Fredericq (106) failed to demonstrate the liberation of a transmitter in the cephalopod heart on stimulation of its nerve supply. Prosser (107) concluded that humoral transmission does not occur in crayfish ganglia.

On the other hand, Benetato & Munteanu (108) detected an acetylcholine-like substance in the venous return from the brain after electrical stimulation of the hypothalamus. Kabat (109) presents evidence of a cardiac inhibitor which is constantly being liberated in the head and transported by the blood. Its chemical identity is unknown, but it is not choline or acetylcholine.

Rats on a choline deficient diet for one to five months developed no deficiency in neuromuscular transmission or in the acetylcholine content of the nerve trunks (110). Lissak & Pasztor (111) analyzed the optic nerve, optic tract, and the saphenous nerve, and found that these afferent nerves contained far less acetylcholine than somatic motor nerves. They do not think that this argues against the cholinergic character of afferent nerves.

The repetition of poorly controlled or badly designed experiments which might have a critical value is an onerous task. Trowbridge (112) has refuted the statement that stimulation of the leg muscles in the frog or cat causes an increase in the cholinesterase content of the venous return from that limb by studying the blood concerned instead of renal venous blood.

Bacq & Heirman (113 to 118) have presented an enormous number of experiments which argue for the physiological importance of adrenoxine. Cannon (119) argues the case for chemical



transmission, as opposed to electrical. Parker (120) discusses the neurohumoral theory of transmission, citing for the greater part, the experiments in which chromatophores were used as indicators. Danielopolu & Marcou (121) present a detailed discussion of the physiological significance of epinephrine, sympathin, and acetylcholine.

*Sensitization.*—The generalization that an autonomic effector is sensitized to its "chemical transmitter" by denervation is strengthened by adding to the long list of tissues which give this response the heart of the cat (122), the fish scale melanophore (123), and the sphincter of the iris (124 to 129). Sensitization of the pupillary constrictor is notable in that acetylcholine is the exciting agent involved, and that postganglionic denervation caused no greater sensitization than section of the third nerve (128). This latter observation is quite different from that described by Hampel (130) for the nictitating membrane. Fatheree, Adam & Allen (131) reported that this difference in sensitization to epinephrine after pre- and postganglionic denervation disappears in time. Atlas (132), however, found that ten months after section of the median nerve and preganglionic sympathectomy of the arm, the differences in skin temperature persisted in the fingers. Those with a postganglionic denervation were cooler and more sensitive to injected epinephrine. This difference in epinephrine sensitivity is irrefutable evidence that the isolated postganglionic neurons exert some influence on the effectors, but Bronk *et al.* (133) and Hare (134) found no evidence of reflex or tonic discharges from decentralized ganglia.

A fallacy in the argument that the sympathectomized iris is more sensitive to ergotamine tartrate than the normal has been revealed by Drake & Thienes (135). Adrenalectomy abolished this difference in response, which was probably due to release of epinephrine by the ergotamine.

When a thyrotoxicosis was induced in dogs, there was, according to Auman & Youmans (136), a sensitization of effectors which are activated by adrenergic nerves, while the tissues inhibited by adrenergic and those supplied by cholinergic neuroeffectors were unaltered. They conclude that there is a differential sensitization of excitatory adrenergic systems, but since the heart is the only organ studied in this category, their generalization has only limited support.

Heim (137) reports that when cats, sensitized with a foreign



protein, were injected three to five weeks later with the same protein, there followed an increased excitability of the effectors innervated by the vagus.

Two theories of the mechanism of sensitization have failed to receive support. The belief that sensitization is due to an increased permeability of the cell membrane which permits an easier entry of the chemical stimuli has been tested by measuring the electrical conductance of muscle cells from normal and denervated nictitating membranes (138). Conductance in the denervated tissue was not increased. The greater effectiveness of acetylcholine after denervation of skeletal muscle has been attributed to a diminution of the cholinesterase activity. Meng (100), however, found no correlation between the enzyme activity and the response to acetylcholine in the denervated rectus muscle of toads.

Stephens (139), in a study of the effects of vasodilator and vasoconstrictor drugs on the spleen, observed that a greater constriction in response to epinephrine was an immediate result of denervation.

#### POSTGANGLIONIC NEURONS

When the preganglionic fibers to the superior cervical ganglion are degenerated, no terminal branches of axons or "synaptic axon-terminations" are present, but when the celiac or inferior mesenteric ganglia are decentralized, some of these structures persist. Kuntz's (140) interpretation is that the celiac and inferior mesenteric ganglia contain reflex connections. Since no details of the "decentralization" are given, an alternative explanation is that not all preganglionic fibers have degenerated. Similar studies after bilateral section of the thoracic and lumbar ventral roots are indicated.

Wolf (141) has reinvestigated the numerical relationship between the preganglionic fibers of the cervical sympathetic trunk and the cells of the superior cervical ganglion. Since Wolf used silver instead of osmic acid preparations of the trunk, he found a lower number of cells for each fiber than reported by Billingsley & Ranson (142). According to Foley (55), some of these trunk fibers are postganglionic, so the true number of cells per fiber is perhaps between the eleven to seventeen found by Wolf and the thirty-two reported by Billingsley & Ranson. In contrast to this extensive termination of each preganglionic sympathetic fiber, Wolf found only two cells for each fiber in the ciliary ganglion.



Physiological information about the synapse between preganglionic sympathetic fibers and postganglionic neurons has run far beyond the anatomical studies. The projection of each preganglionic fiber onto a great many ganglion cells was inferred from the anatomical studies of Billingsley & Ranson (142) and of Wolf (141). But most of the information about the multiple innervation of each ganglion cell is derived from recordings of the electrical activity of a single postganglionic fiber, on successive stimulation of the various preganglionic trunks leading into the ganglion (143). If excitation of the postganglionic neurons is accomplished by a substance liberated by the preganglionic fibers, the more rapid firing of the ganglion cell as more entering fibers are stimulated may signify only the liberation of greater amounts of this exciting substance. The direct relationship between neuronal activity and the concentration of the exciting agent has been demonstrated by perfusing the ganglion with increasing concentrations of acetylcholine (143). This does not imply an histologically demonstrable connection between the discharging preganglionic fibers and the excited ganglion cell. On the other hand, if excitation is effected by some process which depends upon contact of the preganglionic fiber with the ganglion cell, the convergence of this great number of fibers onto each cell should be demonstrable.

An histological method that promises to be of considerable aid in the analysis of sympathetic ganglia is one developed by Nonidez (144). It is a modification of a Cajal block method applied to chloral hydrate fixed tissue, and differentiates postganglionics from preganglionics, afferents, and parasympathetics. With Hare, Nonidez (145) confirmed his original interpretation of this differential argyrophilia by applying the method to denervated ganglia. They are not sufficiently certain of the anatomy of the synapse to tell from Nonidez-Cajal preparations of such isolated ganglia, whether the anatomical basis for a ganglion reflex is present or not, but separation of the sympathetic ganglia of the upper thoracic chain from their preganglionic connections by thoracic ventral root section does deprive them of reflex excitability (134).

The electrical excitability of the normal and denervated superior cervical ganglia in the cat, as determined by voltage-response and voltage-capacity curves, indicates a different excit-



ability for postganglionic cell bodies and dendrites as distinguished from postganglionic nerve fibers. No break was found in similar curves obtained from the cervical sympathetic trunk (146). Since this is so contradictory to the "Chronaxiespektrum" determined by Maltesos & Schneider (147), a few differences in the experimental conditions may be explanatory: Maltesos & Schneider used pupillary dilatation, vasoconstriction, and vasodilatation as indicators of excitation, while Acheson & Simeone (146) used only contraction of the nictitating membrane. A differential in electrical excitability has permitted Parker & Rosenblueth (148) to identify two types of nerves going to the melanophores in the catfish tail. This dual innervation is antagonistic: one group causes concentration, the other dispersion. Similarly Hellauer & Schneider (149), by varying the wave form, intensity, and frequency, demonstrated in the chorda tympani two groups of fibers to the salivary glands in the cat. One kind was concerned with the secretion of salt, the other with mucin. Section of the chorda tympani (150) was found to have only a transient effect on the composition of saliva in dogs.

Conduction velocity in postganglionic sympathetic fibers in man has been estimated by the increases in the latent period of a skin resistance response (151) when the recording electrode is moved distally from the spinal region. Their velocities ranged from 0.85 to 2.17 m. per sec. and are in fair agreement with those of 0.6 to 1.4 m. per sec. more directly determined for postganglionic fibers in the cat (133). One striking peculiarity of their findings is that conduction velocity in the leg is only half that in the arm.

The distribution of postganglionic sudomotor fibers in man is well presented by Guttman (152) in a beautifully illustrated paper. Zones of anhidrosis caused by nerve lesions are sharply defined by the starch-iodine method.

A detailed report of a critical study of the effects of vasoconstrictor nerves on the oxygen consumption of a striated muscle contradicts the earlier experiments of Rein & Schneider (153). According to Pappenheimer (154), the reduction of oxygen consumption during vasoconstriction is only apparent. The injection of epinephrine increased both arteriovenous oxygen difference and arteriovenous temperature difference; stimulation of the vasoconstrictors usually diminished the arteriovenous oxygen difference and always decreased the arteriovenous temperature difference.



Since ergotamine abolishes the effect of nerve stimulation on the apparent oxygen consumption, Pappenheimer suggests that "the action of the vasoconstrictor is to divert the blood from parts of the muscle through regions in which oxygen consumption and surface available for heat loss are small. These regions may be arteriovenous anastomoses."

Coronary blood flow in the heart-lung preparation depends upon mean arterial pressure, but if the heart is accelerated by an electrical excitor, an increase in the coronary flow occurs in the absence of a rise in arterial pressure (155). Stimulation of the sympathetic nerves caused an increase of about 150 per cent in coronary flow, even when there was no rise in arterial pressure. Shipley *et al.* (156) also observed large increases in blood flow through the left coronary on stimulation of the left stellate ganglion. However, the right coronary was little influenced by vagal or stellate stimulation and excision.

Johnson (157, 158) has sharply criticized the rationale of cutting the nerves to the biliary tract to relax the sphincter of Oddi (159). Such denervation was found to retard the evacuation of lipiodol in eight cats.

#### PREGANGLIONIC NEURONS

Since the advantages of preganglionectomy in the treatment of peripheral vascular disease have been recognized, surgeons have been faced with the problem of designing procedures which will effect a complete denervation with minimal regeneration. Unfortunately, there has been little agreement about the preganglionic outflow in man; few direct determinations have been made, and most schema are based upon comparative anatomical data. Sheehan & Marrazzi (160) stimulated the ventral roots of the spinal cord in monkeys and recorded potentials from peripheral nerves. The autonomic nature of these impulses was established in each case by the injection of nicotine, which blocked synaptic transmission in the sympathetic ganglia, and so suppressed the potentials in the peripheral nerve. Since no preganglionic fibers to the monkey's upper extremity were found leaving the cord above the fourth thoracic ventral root, Sheehan & Marrazzi doubted the necessity of cutting the second and third roots in man in order to interrupt all the preganglionic fibers to the hand. Gehegan *et al.* (161), in experiments similar to those of Sheehan & Marrazzi, have



used changes in skin resistance, instead of nerve potentials as an indicator of autonomic activity. This method offers the advantages of avoiding any confusion of somatic and autonomic responses, and of requiring no dissection of the peripheral nerve. With Ray, Geohegan *et al.* have used this method on a large series of patients subjected to laminectomy (162). They have positive evidence that the hand receives preganglionic fibers from T<sub>2</sub> to T<sub>9</sub> inclusive. The upper limit agrees with that found by Smithwick (163, 164, 165, 166), who has observed that excision of ventral roots T<sub>2</sub> and T<sub>3</sub>, in addition to cutting the sympathetic trunk below the third thoracic ganglion, is essential to a complete preganglionic denervation of the hand in man. Wilkins & Eichna (167) state that this denervation may be accomplished by cutting the ventral roots of T<sub>1</sub> and T<sub>2</sub> and the thoracic sympathetic trunk between the third and fourth ganglia. Although this procedure appears to leave the pathway from T<sub>3</sub> intact, they report an absence of sympathetic reflexes in the arm after the operation. Kirgis (168) has described a ramus connecting the second and third thoracic nerves in man, and points out that this is a probable pathway for sympathetic fibers from T<sub>3</sub> to the brachial plexus.

Hyndman & Wolkin (169) have studied the distribution of sweating responses in patients after section of thoracic ventral roots, excision of sympathetic ganglia, and cord lesions. One of their cases is especially informative: after section of ventral roots T<sub>3</sub> to T<sub>9</sub> inclusive, they found no zones of diminished sweating. This suggests that T<sub>10</sub> may contain preganglionic fibers which supply the upper extremity and the thoracic region. The fact that T<sub>1</sub> and T<sub>2</sub> subserve sweating as low as the sixth thoracic segment shows the enormous overlap in preganglionic nerve supply. They suggest (170) that the sweating response to pilocarpine be used as a test for distinguishing pre- from postganglionic sympathectomy, since sweat glands deprived of their postganglionic innervation fail to respond.

Preganglionic denervation of the leg in man is much simpler than a similar denervation of the arm. Atlas (171) has modified the surgical procedure to allow for the variations in the connections of the fourth lumbar ganglion. Merrick (172), from studies on the effects of alcohol injection on sympathetic ganglia and their rami, concludes that paravertebral block can effect a denervation of the extremities and the thoracic viscera by destroying the post-



ganglionic neurons, but that permanent denervation of the abdominal viscera by this method is impossible. In the latter case, since the postganglionic neurons lie in the walls of the viscera, only preganglionic fibers are damaged by the alcohol, and they regenerate rapidly.

The circulatory effects of sympathectomy have been studied by Smith, Allen & Craig (173) who report a decrease in circulation time through the leg after lumbar sympathectomy. Similar acceleration of blood flow was accomplished by heating the leg, and appears to be related to vasodilatation. Gage & Ochsner (174) observed that collateral circulation was better established in the absence of vasoconstrictor fibers, and therefore recommended sympathectomy for the prevention of ischemic gangrene following operations on the large vessels. Atlas (175) has evidence that the development of collateral circulation in the absence of sympathetic innervation may be very slow. In cases of peripheral arteriosclerotic disease, sympathectomy produced no immediate increase in oscillometric readings, but in the course of the next two years there was a gradual improvement in the circulation of the affected extremities. One tissue whose blood supply is diminished rather than increased by sympathectomy is bone, according to Zinn & Griffith (176), who suggest that this paradox may be due to the shunting of blood through the greatly dilated vessels of the soft tissues. The rigidity of bone prevents any comparable dilatation of the osseous vessels.

The application of sympathectomy to diseased circulatory systems has not been invariably successful (177, 178, 179, 180). Corcoran & Page (181) and Adams *et al.* (182) investigated the effects of sympathectomy on renal blood flow in hypertensive patients. Diodrast and inulin clearances permitted estimations of renal blood flow and filtration fractions. Little support was provided for the idea that renal ischemia is the cause of the hypertension or that sympathectomy effectively increases renal blood flow. The slightly beneficial effect of sympathectomy was attributable to a decrease in peripheral vascular resistance. Results quite contrary to those of Corcoran & Page have been obtained by radiography of the renal vessels before and after sympathectomy in the dog (183). Dilatation was the constant result of renal sympathectomy.

The vasodepressor effect of potassium sulfocyanate is apparently due to vasodilatation, and the effectiveness of the drug is increased by the blocking of vasoconstrictor pathways (184).



Vagal and sympathetic control of gastric secretion has been shown by Heslop (185) who measured volume, acidity, and mucus content of gastric juice during stimulation or after section of the nerves. Jennings & Florey (186) centered their attention on the mucous cells of the cardiac and pyloric regions and the mucous neck cells of the fundal glands in similar experiments.

It has been stated that cholinergic fibers with a gastric destination leave the spinal cord over the dorsal roots of  $T_8$  to  $T_{11}$  and course in the greater splanchnics (187, 188). These fibers are motor and when stimulated produce gastric contractions. Previous observations make the existence of such fibers in mammals extremely doubtful.

Sympathetic control of the thyroid has intrigued physiologists for years, but we are aware of no more direct or convincing experiment than that of Helin & Zilliacus (189). Action potentials were recorded from the thyroid during stimulation of the cervical sympathetic trunk or injection of epinephrine into decerebrated cats. This electrical activity was attended by a decrease in the iodine content of the gland of as much as 85 per cent, and an increase in the blood iodine of about 40 per cent. Since the liberation of iodine was always associated with an "electrothyreogram," the electrical response was considered an index of secretory activity.

Our knowledge of cervical sympathetic control of vascular channels has been extended by Biberstein (190) to include allergic phenomena. Sympathectomy increases the local response in allergic and primary inflammatory reactions of the rabbit's ear. The blood vessels of the brain respond by constriction to sympathetic stimulation (54). In partially iridectomized cat eyes, the anterior surface of the lens can be seen to flatten during stimulation of the cervical sympathetic trunk (191, 192). After intracranial damage to the third nerve, the regenerating fibers may or may not re-establish connections in the ciliary ganglion (193). If they do not, the pupil remains dilated and fixed; if they do, the pupillary response is almost invariably abnormal, because of the misdirection of the regenerated axons.

#### CENTRAL NERVOUS SYSTEM

Cortical control of the smooth muscle of the stomach and esophagus has been studied by Hesser, Langworthy & Kolb (194). Using bulbocapnine in lieu of a general anesthetic to ensure minimal depression of autonomic responses, they found that bilateral



excision of the motor cortices resulted in a greater activity and responsiveness of the gastric muscle. A comparable effect on the bladder had been previously described. According to Gardner (195), the centers for voluntary control of micturition are located bilaterally in the frontal lobes in man. His patient was continent of urine after removal of one frontal lobe, but was incontinent after removal of the second.

The control of rage reactions in cats and dogs was localized to the olfactory tubercles, amygdaloid nuclei, and hippocampus-fornix system by Spiegel *et al.* (196). Bilateral lesions in these structures left the animals susceptible to outbursts of rage, while lesions of the neocortex failed to produce this reaction. It is most remarkable that destruction of the olfactory bulbs or stalks, the most obvious afferent path into the hippocampal system, was without effect on the animal's behavior. A partial confirmation of these experiments is provided by Wolf *et al.* (197). The neocortex was removed from each of three cats, and especial care was taken to avoid damage to the olfactory system. Although these cats were active, they never showed any signs of rage, even when handled.

No decisive experiment has appeared which settles the issue of autonomic representation in the hypothalamus. That the anterior part of the hypothalamus is a parasympathetic center and the posterior part sympathetic is established beyond doubt, according to Heslop (185, 198). Working with Beattie, he found that stimulation of the anterior part of the hypothalamus increased gastric secretion and acidity, while excitation of the posterior part diminished the rate of flow and acidity. Benetato (199) also concluded that there were parasympathetic centers in the anterior hypothalamus. He injected acetylcholine into that region and regularly obtained a fall in blood pressure, a response which was abolished or even reversed by atropine.

Weinstein & Bender (200) found a species difference in the diencephalic representation of the pupillodilator mechanism. In the monkey excitation of the sympathetic mechanism is the more important, since section of the cervical sympathetic diminishes or abolishes the dilator response to hypothalamic stimulation; in the cat, inhibition of the parasympathetic mechanism is predominant. Hodes & Magoun (201) found that in the cat the two mechanisms, oculomotor inhibition and sympathetic excitation, had distinctly different topographic representations.



Carlson, Gellhorn & Darrow (202) recorded pupillary, nictitating membrane, galvanic reflex, and blood pressure responses during electrical stimulation of the forebrain in unilaterally sympathectomized cats. Bilaterally equal pupillary dilatation indicated parasympathetic inhibition, contraction of the normal nictitating membrane sympathetic excitation. They found that sympathetic and parasympathetic responses appeared in various combinations.

Since dilatation of the pupil is no longer acceptable as evidence of sympathetic excitation (200, 201, 202, 203), the sign of a vascular response becomes questionable evidence for sympathetic or parasympathetic activity, especially as a fall in blood pressure may be attended by a diminution in the activity of the sympathetic nerves of the heart (204, 205). Depressor responses to diencephalic stimulation associated with a slowing of the heart might, therefore, be caused by an inhibition of the thoracolumbar outflow alone, or by such inhibition plus excitation of the vagus. Recordings of the vagal and sympathetic efferents to the heart would be most helpful in evaluating Wang and Ranson's (206) study of the central control of heart rate. While all of these factors must be considered in evaluating blood pressure responses, responses of the nictitating membrane, piloerectors, and sweat glands have no such ambiguous origin and may be accepted as positive evidence of sympathetic activity (202, 207).

Hare & Geohagan (208) have emphasized the role of frequency of electrical stimulation in determining the character of the response to hypothalamic excitation, but Berry & Hodes (205) feel that the reversals in blood pressure response, which occur when the stimulus frequency is altered, are merely physiological curiosities. They found two types of reversals: one, pressor responses to stimulation within the hypothalamus were converted to depressor responses by lowering the frequency below five per second; and, two, falls in blood pressure during stimulation of areas adjacent to the hypothalamus were only occasionally changed to rises by increasing the stimulus frequency. The first type had a higher voltage threshold than the second.

Since the popularization of stereotaxic instruments for introducing electrodes into the deeper parts of the brain, experimentalists have devoted careful attention to the exact location of their sites of stimulation. This overemphasis on localization has led to a relative neglect of the characteristics of the stimulus, and very



few papers include any mention of frequency, wave form, duration of pulse, voltage, or current flow. When the voltage is recorded, it is often not clear whether the peak was measured under load or not, a matter of great importance when stimulators of high source impedance are used. Aida & Geohegan (209) have attempted to find the optimal electrical stimulus for hypothalamic excitation, and have used the magnitude of the pressor response as an indicator. Their stimulator delivers impulses of 0.03 to 100 msec. duration at frequencies of 1 to 20,000 per sec. over a wide voltage range and with a variety of wave forms. Wave form, voltage, and frequency could be varied independently, and all measurements were made under load. In a cat anesthetized with Dial, the same point in the hypothalamus was activated with a great variety of stimuli. It was found, in a series of such experiments, that a square wave pulse of 120 to 240 cycles per sec. was most effective. The greatest responses were obtained when the pulse lasted for half, or slightly less than half, of the cycle; any increase or decrease in duration diminished the response.

The hyperglycemia produced by morphine in normal but not in sympathectomized cats has been studied by Brooks, Goodwin & Willard (210), who have localized the responsible mechanism in the posterior part of the hypothalamus.

The part played by the cerebral cortex in pupillary dilatation following the injection of drugs has been studied by Girndt & Evers (211) in uni- and bilaterally decorticated cats. Only atropine produced a greater effect in the operated than in intact animals.

The metabolic disturbances that follow hypothalamic lesions are receiving an increasing amount of attention. Brobeck & Long (212) found no alleviation of diabetes mellitus in partially depancreatized rats. Keller (213) was unable to relate the decrease in insulin tolerance in cats to either the location or the extent of hypothalamic lesions, and suggests that pituitrin may be the anti-insulin factor involved. Instead of making lesions in the hypothalamus and studying effects on carbohydrate metabolism, Hasama (214) has chosen to record the electrical activity in different parts of the hypothalamus before and after altering the animal's blood sugar. He has applied the same technique to localizing heat regulating mechanisms (215), and to studying autonomic responses to labyrinthine stimulation.

Disturbances in fat metabolism, resulting in marked obesity, have been reported following hypothalamic lesions in the rat (216,



217, 218) and in the dog by Bruhn & Keller (219). Metabolic studies on these fat rats (218) indicate a lowered basal oxygen consumption and a higher R. Q. during the absorption state. Apparently the most important factor in the obesity was the enormous increase in appetite; the rat with hypothalamic lesions would eat twice as much as its littermate control. When pair fed with its control, the voracious rat gained weight only slightly more rapidly than the normal. Hetherington (217) found, however, that the greatly reduced spontaneous activity was probably more responsible for the obesity than the increased food intake. Bruhn & Keller (219) reported that the heat production increased as their dogs became obese. A nice correlation was found between weight and water exchange in these polyuric animals; water exchange per unit of body weight remained constant as the obesity progressed.

Hypothalamic lesions abolish or greatly reduce sexual activity in male guinea pigs, though no explanatory changes appear in the gonads or accessory reproductive organs. The lesions are effective apparently because they interfere with some neural rather than hormonal mechanism (220, 221, 222, 223). Griffiths (224) reported two human cases so completely eunuchoid that they simulated cases of early castration. Autopsy revealed hypothalamic tumors which, because of their suprasellar position, had not destroyed the anterior lobe of the pituitary.

The origin of gastrointestinal ulcers from lesions of the central nervous system is supported by both clinical and experimental data (225). Post-mortem examination of 118 ulcer cases revealed hemorrhage of the brain or meninges in 32 per cent and some form of brain softening in 20 per cent (226). A few days after a cerebral hemorrhage, an hemorrhagic infarction of the mucosa may appear which in two to four weeks becomes a typical peptic ulcer (227). Autopsies of 246 monkeys (228), many of which had lesions in the central nervous system, disclosed gastric ulcers in 10 per cent. There was no correlation between the incidence of ulcer and type of lesion, but unfortunately this series did not include any animals with hypothalamic lesions. The best correlation of ulcers was with loss of weight. Lium (229) provides evidence that the sympathetic system is somehow related to gastrointestinal ulceration. Excision of the celiac and mesenteric ganglia resulted in peptic ulcers in four of nine dogs, all of which had a diarrhea with blood and mucus in the stools.

Kessler (230) concludes from studies on cats and monkeys that



the hypothalamus is essential for emotional display, and that the stuporous state of an animal with a bilateral hypothalamic lesion is not due to a block of the afferent paths to the cortex. Lesions in the ventral part of the thalamus cause the animal to have a labile temperament. Gellhorn and his associates (231 to 241) have published a large number of papers on the interrelations of emotions, autonomic activity, and environmental conditions.

Chatfield (242) explored the medulla in cats to locate the salivatory mechanisms. Responsive areas were in the reticular formation and along the facial and glossopharyngeal nerves. Corbin, Harrison & Wigginton (243) observed that they always got salivation when they obtained pseudomotor contractures of the tongue in response to intramedullary stimulation. Their responses were elicited from the intramedullary course of the seventh nerve, the reticular formation near it, and from the chorda tympani fibers peripherally.

The spinal apparatus influencing temperature regulation in the cat has been studied by Clark (244) in a series of cats surviving transection of the lower cervical cord. These cats were unable to adjust to sudden exposure to cold, but could slowly acclimate themselves to gradual reductions in environmental temperature. While Clark's reasoning that the slow compensation to cold represents an increase in metabolism is logical, it is unfortunate that he has to use inferential evidence. A careful study of heat loss and heat production at different environmental temperatures in such preparations might profitably be made with Day & Hardy's (245) heat flow calorimeter, which was designed for studies on premature infants.

#### REFLEXES

*Vasomotor reflexes.*—Elimination of the vasoconstrictor impulses of the thoracolumbar outflow causes a pronounced and prolonged vasodilatation; there is, however, a gradual increase in blood pressure, so that in dogs with both sympathetic chains completely removed, the arterial pressure may be restored to normal (246). The rapid readjustment of blood pressure, reported by Herman *et al.* (247) after destruction of the spinal cord with a curette, would be more convincing if such restoration of normal blood pressure had been observed after excision of the cord. Ether is an extremely powerful vasodepressor in the sympathectomized dog.



Root & McAllister (248) have found that the vasoconstrictor outflow must be intact farther caudally than the sixth thoracic segment, and must also be under suprasegmental control for the maintenance of a normal blood pressure under ether anesthesia.

A chronic hypertension, on the other hand, is caused by eliminating depressor afferents when the carotid bifurcation and cervical aortic depressor nerve are excised (249). The maximum duration of this hypertension was greater than three years. The carotid sinus pressor receptors become active by the third month of fetal life in the sheep, and increase in responsiveness with each successive month. By the second half of fetal life, stimulation of the carotid sinus causes vasomotor and cardiac responses comparable to those obtainable in the adult (250).

Von Euler, Liljestrand & Zotterman (251, 252) have suggested revisions of the present concepts of carotid sinus innervation. They now regard the sinus region as a peripheral "nervous center" comparable to the retina and the olfactory mucosa. Apparently a synapse is interposed between the receptor and the afferent nerve fiber, because 5 to 10  $\mu$ g. of acetylcholine injected into the external carotid artery causes a burst of activity in the finer fibers of the carotid sinus nerve. Acetylcholine is known to facilitate interneuronal transmission, but it is not known to have an excitatory action on receptors. Furthermore, ganglion cells are present in the vicinity of the carotid sinus. They have also found small impulses in the potential records of the sinus nerve which respond to variations in pressure within the sinus, but are unresponsive to chemical stimuli and synaptotropic agents. Because of their numerical superiority over the big impulses, they are considered important in pressure reflexes from the carotid sinus. Only the chemical receptors are supposed to have a peripheral synapse; the pressor receptors seem to have a conventional arrangement.

Perhaps the same events in the carotid sinus region which von Euler *et al.* have described are responsible for the respiratory stimulation observed by Koppanyi & Linegar (253) after injection of acetylcholine. Their interpretation is that direct excitation of the chemoreceptors is responsible; von Euler *et al.* attribute the effect to facilitated synaptic transmission.

The role of the pressor receptor nerves in the vasomotor response to postural changes was demonstrated by recording blood pressure changes as dogs were tilted from the horizontal to the



vertical position (254). Denervation of the carotid sinuses and cutting the aortic depressor nerves eliminated the vasomotor adjustments; in some cases assumption of the vertical position caused the blood pressure to fall to shock levels. Stead & Ebert (255) have made similar observations on patients with postural hypotension. Plethysmograms of the hands of hypotensives showed no vasoconstriction as the patients were elevated into an upright position; normal subjects regularly responded with vasoconstriction. They suggest that hypotension is, therefore, a disease of the sympathetic nervous system, but without evidence of abnormal sweating or piloerector responses, it seems just as reasonable that the fault is in the pressor receptors.

Grimson & Shen (256) have found that carotid sinus stimulation causes vasoconstriction in normal and in skinned hind legs. They concluded, of course, that the vessels of the skeletal muscles were responsive to vasomotor impulses. In contrast to this, Friedlander, Silbert & Bierman (257) have decided from temperature studies in man that the circulation in the skin and muscles of the extremities is independently regulated, and that the blood flow in the muscles is not directly controlled by the sympathetic nervous system. Stimuli which caused changes in skin temperature, caused no change of temperature in the muscles. An alternative explanation is that temperature measurements deep within the muscle are not indicators of blood flow. The use of a heating unit, operating at a temperature higher than that of the blood, which cools as blood flow increases, might reveal a reflex nervous control of the skeletal blood vessels. Barcroft & Miller (258) found it advantageous to heat the extremity, by immersion in hot water, to create a sufficient temperature difference between the tissue and the general body temperature. This might cause sufficient dilatation to mask effects of other vasodilating stimuli. It is true that vasomotor changes are greater in the hands and feet than in the arms and legs (167, 259, 260), but such direct experiments on blood flow in skeletal muscle as those made by Pappenheimer (154) leave no cause for doubt that it is under control of the vasomotor nerves.

A deficiency of oxygen in the inspired air affects circulation and respiration through a reflex originating in the chemoreceptors of the carotid bifurcation and in the aorta (261). In decerebrated animals the response is slight if present at all, a fact which indicates its integration at least at diencephalic levels. When the afferent



paths of the reflex are destroyed, the oxygen lack directly depresses both the vasomotor and respiratory centers.

Mies (262) and Bungardt (263) have suggested that a local narcosis of an afferent nerve may augment its response to stimulation. Mies used the aortic depressor nerve and blood pressure changes for testing this idea.

A deficient venous return is an effective stimulus to afferents in the heart, especially in the atria, which reflexly cause an increase in arterial pressure and a generalized vasoconstriction (264). Respiratory reflexes may also be activated, but this response is attributed to a sensitivity of similarly located afferents to an excess of oxygen in the inspired air and to pH changes in the blood. A reflex zone in the superior vena cava has also been described (265). An ingenious and direct test for vascular reflexes initiated by distension of the superior vena cava is described by Ballin (37). A cannula small enough to be inserted through the right external jugular vein, contained in its tip a number of ribs which could be spread in umbrella fashion. Clotting was prevented with heparin. Even in the unanesthetized dog, distension of the superior vena cava at its junction with the right atrium caused no significant change in heart rate or arterial pressure. The receptors for the Bainbridge reflex are apparently not in this part of the venous system.

Pressor responses to neosynephrine or pitressin initiated a reflex mediated by the left vagus which produced heart block in dogs (266). Other efferent paths to the heart were excluded by sympathectomy and section of the right vagus. When the right vagus was left intact and the left cut, an elevation of the blood pressure caused slowing of the heart but no block. A sharp lowering of the blood pressure by nitroglycerine or acetylcholine is opposed by a reflex liberation of epinephrine (267). If the adrenals are demedullated, these depressors still cause an acceleration of the decentralized heart, probably because of a reflex liberation of sympathin by adrenergic nerves.

Greene (268) has observed a reflex dilatation of the coronary vessels during skeletal muscle activity under light ether anesthesia. Atropine also causes an increase in coronary flow, but only if the vagal nerves are intact. Sympathectomy does not interfere with the response, apparently because it is due to the blocking of vagal impulses by the atropine (269).



Circulation is influenced not only by reflexes whose afferents are within the vascular system, but also by those with an exteroceptive origin. Evidence that these vasoconstrictor reflexes act principally on the small arteries and arterioles has been provided by Hertzman (270) in experiments on the hand. Kuntz & Haselwood (271) found that the intestinal blood vessels of the decerebrate cat responded to thermal stimulation of the skin: warming caused vasodilatation, cooling caused constriction. Reflex dilatation of the visceral blood vessels has been studied by Anderson & Ekström (272) and by von Reis & Sjöstrand (273) after application of chemical irritants to the skin. The number of blood-filled capillaries per sq. mm. of tissue was used as their criterion of vascularity.

Hertzman, Roth & Dillon (274) found that usually the vasoconstriction in a cooled finger is greater and more prolonged than that in the other fingers. However, their data does not show whether this greater response is due to "local sign" in the vasomotor reflex or to the direct effect of cooling on the local blood vessels. A distinct vasomotor gradient exists from the face to the hands and feet, with the minimal vasoconstriction in the face (275). This gradient is more fully realized in attempts to produce reflex dilatation than in observing basal skin temperature.

Heat applied to the skin may be as effective a stimulus for vasodilatation as cold is for constriction. When a cuff, inflated to a pressure of 250 mm. Hg., was applied to the proximal part of the arm or leg, Duthie & McKay (276) found that immersion of that extremity in water at 45°C. caused a vasodilatation in the other extremities. This occurred without any rise in body temperature and is clearly not dependent upon the return of heated blood to a central mechanism.

*Sweating.*—Hyndman & Wolkin (169), using the starch-iodine test, observed that if a sympathectomized arm is flexed, moisture will appear in the antecubital fossa, the palm of a clenched hand will become wet, or if the hand is placed on the ipsilateral shoulder, both surfaces of the skin in contact become moist. While they are aware of insensible water loss through the skin, they do not seem to think it worth while to distinguish between this form of moisture and sweat. Their assumption that the sympathectomized skin was sweating is scarcely justifiable without discriminating evidence. This they call first order sweating; spinally controlled



sweating is of the second order, while third order sweating is of central origin. They have used sweating of the second and third orders in response to heating for defining areas of sympathetic paralysis after various nerve lesions, and in testing for regeneration. They consider this method of testing for sympathetic activity more reliable than skin resistance measurements or psychogalvanic reflexes, because the thermoregulatory sweating depends upon central impulses. So, of course, do skin resistance and psychogalvanic reflexes. It would probably be more fruitful to use all three methods, rather than any one to the exclusion of the others.

According to Carmichael *et al.* (277), reflex changes in skin resistance in man have their origin in two phenomena, sweating and vasoconstriction. If either of these responses is eliminated, the resistance change is diminished, but its abolition requires the suppression of both. Sweating may, of course, be produced by warming, but it is notable that warming facilitates reflex changes in skin resistance. If a subject is adequately warmed, skin resistance changes may be obtained from almost the entire body surface.

*Pupillary reflexes.*—The reflex mechanism of pupillary dilatation has been thoroughly studied by Hodes (203), who confirms the earlier observations of Ury & Gellhorn (278) and of Seybold & Moore (279). Inhibition of the oculomotor nerve is well established as the cause for emotional and reflex dilatation, and in part, for dilatation resulting from central nervous stimulation. The potentialities of the sympathetic and epinephrine are not minimized, but their exclusion does not prevent pupillary dilatation.

*Gut reflexes.*—The intestinal tract may be activated by the application of ice to the abdominal wall or by the ingestion of hot water; conversely, warming the abdominal wall or the ingestion of iced water inhibits the gut (280). Distension of the urinary bladder also reflexly affects the gut (281); the presacral nerve provides the afferent path from the bladder. Local distension of the gut, either normal or deprived of its extrinsic nervous connections, may elicit motility (282). However, when the nervous connections are intact, filling the gut with a standard amount of fluid seems to cause both excitatory and inhibitory reflexes, so that the response is a balance of the two. Stimulation of the central end of the sciatic causes an inhibition of the gut in most cases, even after the splanchnic nerves are cut. Hodes (283) interprets this as a diminution in the basal activity of the vagal nerves, and presents it as evidence of recipro-



cal innervation of the gut. While this is probably correct, simultaneous recordings of the electrical activity of the vagus nerve and the motility of the gut under the conditions of his experiment would give a clearer answer. Hodes, with Berry (205), has already applied this technique to the analysis of vasomotor responses to hypothalamic stimulation.

Distension of the gut in dogs regularly caused respiratory responses (284) which were not abolished by vagotomy but were eliminated by transection of the cord at the first thoracic level.

The finest analysis of the effects of vagal afferents on respiration is that of Larrabee & Knowlton (285, 286), who, by recording the activity of individual nerve fibers, have classified the fibers from the lungs according to their threshold and adaptation. By recording at the same time the efferent impulses from single phrenic fibers, they determined the influence of each group of vagal afferents upon the respiratory responses.

*Other sympathetic reflexes.*—In a well documented and illustrated paper, Chang *et al.* (287) describe the central connections traversed by impulses between their entrance over the vagus nerve and their exit through the pituitary stalk. Similar material is presented in his contribution to the Hess Festschrift (7).

Heymans & Delanois (288) observed a metabolic stimulation following excitation of the pressoreceptors in the carotid sinus.

Sympathetic innervation of the anterior lobe of the pituitary is well established anatomically [see bibliography of Brooks & Gersh (48)]. The physiological evidence is not so convincing, but it is strengthened by the experiments of Phillips, who recorded action potentials from the anterior lobe during stimulation of the cervical sympathetic trunk (289). The passage of fibers from the hypothalamus into the pars distalis or tuberalis has been described by Brooks & Gersh (48) and by Roussy & Mosinger (49).<sup>1</sup> The latter includes a suggestion that fibers which pass directly from the hypothalamus to the anterior lobe may be the efferent path for the reflex activation of the pituitary by light. Browman (290) provides some evidence for this relationship in a report of

<sup>1</sup> One of us has attempted without success to demonstrate this generous nerve supply to the pituitary described by Roussy & Mosinger. Large numbers of fibers from the hypothalamus to the anterior lobe have been seen only in cats and dogs which have survived section of the pituitary stalk for two or more years. These fibers are seen in such disarray that they immediately suggest a neuroma. (K.H.)



the diminished gonadal function in male rats after bilateral removal of the eyeballs. His explanation of this hypogonadism is that the optic enucleation prevents the discharge of impulses from the retina to the anterior lobe by way of the hypothalamus. More direct evidence might be obtained by recording action potentials from the pituitary when the retina is illuminated, similar to those obtained by Helin & Zilliacus (189) from the thyroid, and by Phillips (289) from the pituitary, on stimulation of the cervical sympathetic trunk. Fiske (291) has reported a more rapid sexual development in female rats kept in the light than in controls kept in the dark. Although she does not speculate about the nervous mechanism, she attributes the sexual precocity to stimulation of the pituitary.

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DEPARTMENT OF ANATOMY  
CORNELL UNIVERSITY MEDICAL COLLEGE  
NEW YORK CITY, NEW YORK



## SENSE ORGANS

BY H. K. HARTLINE

*The Eldridge Reeves Johnson Research Foundation  
University of Pennsylvania  
Philadelphia, Pennsylvania*

This review deals with the literature on sensory physiology which has appeared during the past year. Because of the large volume and wide range of this material it is obviously not possible for one individual to cover all phases of the work in equal detail and fairness. The personal interests of the author are necessarily reflected in the choice of material and point of view.

### VISION

*Energy at threshold.*—One of the most fundamental problems in sensory physiology concerns the exchange of energy between the environment and the sense organ. Photoreceptors are ideal for the study of this general problem because of our extensive knowledge of the photochemical reactions which are the first step in the translation of the stimulus of light into nervous action. The recent work of Hecht, Schlaer & Pirenne (1), in which they measured the energy of a flash of light which could just be seen, provides an elegant attack on this problem. They tested completely dark adapted human subjects with flashes of light ( $\lambda = 510 \text{ m}\mu$ ) on a small area in the peripheral retina. The energy that was required for the flashes to be visible was found to be  $2.2$  to  $5.7 \times 10^{-10}$  ergs, measured at the cornea. This equals 58 to 148 quanta of light. Corrections were estimated for losses in the ocular media and for failure of the incident light to be completely absorbed by the visual purple present in the dark-adapted retina. The corrected value for the threshold energy absorbed by the rods was five to fourteen quanta. When the average energy content is so low, individual flashes will not all contain the same number of quanta and consequently cannot all have the same visual effect. The authors found that the frequency with which flashes were seen varied with their average energy content in the manner predicted by statistical theory, assuming that a flash was seen only when the number of quanta it contained equalled a fixed number required to produce a threshold effect. The shape of these distribution curves, moreover, was character-



istic of the number of quanta required even after allowance for fluctuations in the sensitivity of the observer from moment to moment. This furnished an independent estimate that five to seven quanta were required at threshold, which is in excellent agreement with the corrected values of the absolute energy measurements mentioned above. Since the retinal area illuminated included about five hundred rods, the chances that one rod received more than one quantum were small. The authors conclude that a single quantum, which can activate one molecule of visual purple, is sufficient to excite a single rod cell; about six rods must be excited to elicit a threshold effect.

*Visual pigments.*—The threshold of human vision is thus very close to the absolute minimum imposed by the particulate nature of light. This remarkable sensitivity is dependent on the presence of sensitive photolabile substances in the retina. The chemistry of these substances and the metabolic processes that insure their adequate supply are of fundamental importance in the physiology of vision.

Broda, Goodeve & Lythgoe (2) have computed the chromophore concentration in a solution of visual purple from the optical density and the weight of the protein. They conclude that there are ten chromophores per molecule of protein, with a "carrier" weight of 26,500. They estimate that there are  $10^9$  chromophore groups of visual purple in the outer limb of each rod.

The chemical composition of the visual systems of fishes has been shown by Wald (3) to be correlated with their salinity requirements. Terrestrial vertebrates and most marine fishes had previously been found to possess rhodopsin-vitamin  $A_1$  in their retinas, while true fresh-water fishes possess porphyropsin-vitamin  $A_2$ . Wald has now found that fishes capable of existence in a wide range of salinities (euryhaline) contain mixtures of these two systems.

Solutions of "cone-substance" extracted from the retinas of frogs are reported by von Studnitz (4) to be bleached by red light (which did not bleach extracts of visual purple) as well as by white and green light (which caused visual purple to bleach to visual yellow). Both substances were found to regenerate from bleached solutions in the absence of light.

Zewi (5) reports that the rate of regeneration of visual purple in the retinas of live frogs was accelerated by injection of pilo-



carpine, and slowed by atropine, provided the temperature at which the frogs were kept was high (22°C.). At 8°C. neither drug had any detectable effect.

Stenius (6) describes the staining by platinum chloride of visual purple in the outer limbs of rods of the frog's retina. Greenberg & Popper (7) examined sections of the retinas of albino rats by the fluorescence microscope and could identify vitamin-A fluorescence in the pigment epithelial cells in light adapted eyes. In dark adapted eyes there was no vitamin A observable, or only a trace. Animals kept on a diet deficient in vitamin A showed a possible decrease of the fluorescence, but never a complete absence of it, even in severe deficiency.

*Vitamin A and dark adaptation.*—Vitamin A is a precursor of the photosensitive pigments upon which the sensitivity of the eye depends. It is now familiar knowledge that this provides the explanation of the impairment of visual sensitivity usually associated with disturbances in the metabolism of this vitamin. The role of vitamin A in the dark adaptation of human subjects has received careful study by Hecht & Mandelbaum (8). In their experiments both the rod and the cone thresholds were raised as a result of a vitamin-A-deficient diet, the rods being more affected than the cones. A slow but steady rise in threshold usually began shortly after starting the deficient diet; some of the subjects, however, showed a markedly delayed onset of the effect. Partial temporary recovery as the result of a single large dose of vitamin A was shown by some individuals but not by others. For all of the subjects complete and permanent recovery of the visual threshold upon returning to an adequate diet was slow, for some much more so than for others. These variable reactions to vitamin A are undoubtedly part of the reason for the conflicting results that have been reported in similar studies, although inadequate instruments and faulty technique are to blame in some cases.

Mandelbaum (9), in an extension of the foregoing work, has reviewed the principles and methods of measuring dark adaptation, and there is no longer any excuse for reports, clinical or otherwise, that do not measure up to the technical standards set by these papers (cf. 10). Mandelbaum measured final thresholds for various locations of the test-patch on the retina out to 20°. The lowest rod thresholds were found at 20°; the cone thresholds showed little change with visual angle. He found that illumination



of one eye had no effect on the threshold of the other. Various drugs tested (strychnine, amphetamine, caffeine, phenobarbital, morphine) had no demonstrable effect on the course of dark adaptation; alcohol, however, caused a proportionate increase of all thresholds.

Patek & Haig (11) found that oral administration of thyroid extract and of dinitrophenol speeded up dark adaptation in mild cases of night blindness. They suggest that these substances facilitate the utilization of vitamin A by the visual mechanism.

The influence of the intensity and duration of the preadapting light on subsequent dark adaptation of human subjects has been studied by Haig (12). Strong light adaptation, in addition to causing a large loss of initial sensitivity, is known to result in a greatly slowed rate of recovery. Haig's results show that this is just as true following short exposures to very bright light as following long exposures to weaker light. Equal degrees of light adaptation, as measured by the threshold determined at the beginning of dark adaptation, resulted in identical recovery curves regardless of how the light adaptation was achieved. This is contrary to the finding of Wald & Clark (13) that long periods of light adaptation caused a slowing of recovery which was out of proportion to their effect on the initial threshold. Haig ascribes this discrepancy in part to the fact that in his experiments the size of the pupil was fixed, while in Wald & Clark's it was not. The interpretation of these subjective observations is based on the known properties of bleaching and regeneration of the photosensitive substances responsible for the initiation of the visual act.

*The visual receptor cell.*—The chemical reactions induced by light lead to the initiation of nervous activity by the receptor cell. In a sufficiently primitive eye, such as that of *Limulus*, this activity may be recorded by the standard methods of electrophysiology. This reviewer has recently summarized (14) the results of studies on the discharge of impulses in single optic nerve fibers of *Limulus*. The regular trains of nerve impulses elicited by illumination of the eye are characteristic of receptor activity in general; in addition, properties of the visual sense cell which reflect its basic photochemical mechanism are clearly evident.

The alterations in sensitivity of *Limulus* photoreceptors during the course of light adaptation have been followed by Riggs & Graham (15), and the recovery of sensitivity following exposure to



light, by Hartline & McDonald (16). The course of recovery following various degrees of light adaptation showed essentially the same features of the dark adaptation process that are known from experiments on human subjects (12, 13). Ability to undergo light and dark adaptation is a property of the visual receptor cell. This property is due in large measure to the bleaching and regeneration of the photosensitive substance in the sense cell.

The receptor processes intermediate between the primary photochemical reactions and the ultimate discharge of nerve impulses are still far from being understood. A paper by Riggs (17) has a direct bearing on this problem. He found that the sensitivity of the *Limulus* receptor cell fluctuated cyclically with each impulse discharged during the response to steady illumination. The sensitivity measured by the ability to respond to an added flash of light, was found to be lowest immediately after the discharge of an impulse and to rise steadily to a maximum at the time when the next impulse in the steady discharge was expected. This is clearly in agreement with currently accepted general views as to the probable origin of rhythmicity in sense organs. It is to be hoped that recent work on the rhythmic local responses originating in chemically altered regions of peripheral nerve and giving rise to trains of propagated impulses (18, 19) will aid in the solution of this fundamental problem of sensory physiology.

*Ganglionic and retinal mechanisms.*—The integration of the sensory messages from the receptor cells by the higher neurons of the visual pathway is amenable to study by direct observation of the electrical activity of these neurons. The fibers of the optic nerve of *Limulus* discharge impulses only while light shines on the eye, but a microelectrode in the optic ganglion of this animal detected activity in certain neurons only in response to cessation of illumination (20). Ganglionic mechanisms can thus alter the form of the optic response, in this case giving rise to pure "off-responses" closely resembling those observed in certain of the optic nerve fibers of vertebrates. It is at least permissible to postulate similar mechanisms in the vertebrate retina to account for the different kinds of response to retinal illumination observed among different optic nerve fibers (14, 21, 22, 23).

The functioning of the visual pathway is subject to the same general principles that apply throughout the nervous system. Thus convergence and spatial summation are known to take place in the



vertebrate retina. Their role in the excitation of individual retinal ganglion cells has been analyzed by recording the discharge of impulses in single optic nerve fibers from the eyes of frogs (24, 25). Exploration of the retina with a small spot of light was found to elicit responses in a particular optic nerve fiber only if the light fell within a certain restricted region of the retina (the receptive field of the fiber). For a particular optic nerve fiber sensitivity to light, or to small movements of the retinal image, was found to be maximal over the central portion of the fiber's receptive field, but usually extended over a region approximately 1 mm. in diameter (for fibers from the peripheral retina). The receptive field of an optic nerve fiber thus covers an area on the retina much greater than that occupied by a single rod or cone; a single retinal ganglion cell can receive excitatory influences over convergent pathways from many receptor elements. This convergence is the functional basis for the spatial effects observed in the vertebrate retina.

An important consequence of retinal convergence is the spatial summation that takes place over the receptive field of a retinal ganglion cell. It was observed that the discharge of impulses in a single optic nerve fiber depended upon the area of retinal illumination, as well as upon the intensity of the stimulating light (25). Illumination of a large area within the fiber's receptive field was always more effective than illumination, at the same intensity, of any subdivision of this area. Summation of subliminal effects also occurred. This, it has been seen (1), is a factor in determining the lower limit of human vision.

The retinal mechanisms concerned with color vision have been explored by Granit, who recorded the activity of retinal neurons in the eyes of various vertebrates with the aid of a microelectrode. With a microelectrode oscillograms can be obtained in which the activity of individual retinal ganglion cells can be discerned clearly (21, 22, 23). Even when this is not the case, the recorded responses will be contributed by relatively few units; such records are useful though not so valuable in the analysis as those showing clear-cut single neuron responses. Granit is not always explicit as to how much "restriction" his microelectrode has achieved in specific experiments. Evidence of a mechanism for color reception has been reported for the albino rat (21). Measurements were made of the relative energies of monochromatic lights of various wave lengths necessary to produce a constant response (threshold, or cessation



of flicker). The visibility curves obtained from some of the preparations were simple in character and resembled closely the absorption spectrum of visual purple (maximum at 500  $m\mu$ ). For others (some of which were almost certainly single neurons) the curves had a secondary maximum in the red (*ca.* 600  $m\mu$ ), which was markedly accentuated, relative to the maximum at 500  $m\mu$ , by light adaptation. The fact that the two maxima were differently affected by light adaptation leads the author to speak of red and green "substances," "elements," and "curves." Likewise in the retinas of frogs and fishes (26) single neurons (or small numbers of them) showed visibility curves that were distinctly shifted towards the red after light adaptation, and that showed differences among individual elements in the positions of their maximum sensitivity in the spectrum.

Elements were also found in the frog's retina having a maximum of sensitivity far out in the blue, and in the guinea pig some of the preparations gave visibility curves similar to the absorption spectrum of visual purple, while others had a distinct secondary maximum at 450  $m\mu$ . In the tortoise most of the elements studied individually showed a maximum sensitivity at 600  $m\mu$  which was unaltered in position during light and dark adaptation (27). To judge from a statement made elsewhere (26), the average sensitivity of the tortoise retina, determined by less restricted recording, was farther towards the green. There can be little doubt from these experiments that the retinas of animals thought to possess at least some ability to distinguish color contain different elements which show a diversity of spectral properties that can explain color vision.

*Subjective measurements.*—Subjective phenomena of vision depend upon the properties of the individual receptor cells, the nervous organization of the retina, and the integrating action of the higher centers. These aspects of the visual mechanism are intimately related. In well designed experiments, however, it is frequently possible to make reasonable interpretations which distinguish between them. Thus properties of the visual receptor cell, due principally to its photochemical mechanism, apparently dominate the course of light and dark adaptation in human subjects as has already been described.

In brightness discrimination, properties of the receptor mechanism are also evident. Keller has found that brightness discrimination depends on the duration of exposure of the increment in



intensity (28). For short durations only the total quantity of light that had been added to a field of fixed intensity determined whether it could be seen. The amount required at different intensities could be explained in accordance with previously established photochemical theory (29). For long durations the quantity utilized in seeing was governed by a "critical duration." A "critical duration" is also one of the characteristics of visual receptor cells. Keller found that the "critical duration" varied with the level of brightness; this must consequently be taken into account in the quantitative treatment of brightness discrimination.

On the other hand, the area of the retinal image influences brightness discrimination (30, 31). Graham & Bartlett (30) interpreted their data by considering both the photochemical mechanism of the receptor cells and the spatial summation which occurs even in foveal vision. Assumption of a simple law governing the integration of excitatory effects over the illuminated area accounted for their observations quantitatively.

Spatial factors may also be important in the measurement of dark adaptation. Crawford (32) found that the course of dark adaptation depended on the size of the retinal area illuminated during the previous light adaptation. Simple photochemical considerations alone are not adequate to account for this observation.

Factors which affect nervous function in general may influence visual performance. McFarland & Forbes (33) found that breathing mixtures low in oxygen reduced visual sensitivity in human subjects. The course of dark adaptation was not affected by oxygen lack, as the thresholds were all raised proportionately. Breathing pure oxygen restored the threshold within 2 to 3 min.; ingestion of glucose almost completely counteracted the effects of low oxygen. Insulin hypoglycemia also resulted in higher thresholds, and this could largely be counteracted by breathing pure oxygen. The authors suggest that the decreased light sensitivity was due to lowered rates of oxidation, which affected the nervous tissue of the visual mechanism rather than the photochemical processes.

*Additional studies on vision.*—Additional papers that have not been included in the foregoing discussion require mention.

The color vision of chimpanzees and human subjects has been compared in a series of papers by Grether. In their spectral limits (34), their hue discrimination (35), color mixture requirements (36), and spectral saturation curves (37), the chimpanzees were



closely similar to normal human subjects, except for a somewhat weaker "red" mechanism.

The ability of rhesus monkeys to distinguish a striated field from a homogeneous one was only slightly poorer than that of human subjects (38). Comparison of visual acuity on the basis of size of the retinal image shows it to be highest in man, rhesus monkey, and the chimpanzee, which were all similar. It proved to be distinctly poorer in birds and rats (39).

Valuable data on flicker are provided in a series of papers by Crozier & Wolf. A lizard, *Phrynosoma* (40), and a bird, the zebra finch (41), both possessing pure cone retinas, gave simple curves when fusion frequency was plotted as a function of intensity. Data from human subjects (42, 43, 44, 45) showed evidence of contributions by both rods and cones, in accordance with earlier findings (cf. 29). This reviewer regrets that he is unable to grasp the essentials of the theoretical discussions in these papers; for this it is evidently necessary to give careful study to the voluminous reports published by these authors in previous years.

Ludvigh (46) reports the effect of decreased contrast on visual acuity, which was especially noticeable when the contrast was low.

Ingenious proof of the peripheral origin of visual after-images is given by Craik (47). Both positive and negative after-images could be observed with an eye which, during the exposure to the exciting light, had been temporarily blinded by retinal anoxemia induced by pressure on the eyeball.

Craik (48) made direct measurements of the brightness of the retinal image in excised cat eyes for different positions in the pupil of a small pencil of light. The marginal zones of the pupil did not attenuate the light excessively. The differences he observed were too small to account for the observations of Stiles & Crawford (49) on which they based their conclusions that the retina possesses a directional sensitivity.

An interesting, though not especially relevant analogy to the visual receptor is based on the commonly observed sensitivity to light of a glow-discharge tube in a circuit capable of relaxation oscillations (50). The author evidently was unaware of what is actually known about the discharge of impulses in optic nerve fibers.

Granit (51) reports spontaneous activity in the mammalian retina, with fluctuations of sensitivity of single elements and "rotation" of activity among many. Bernhard & Skoglund (52) report



the suppression by ethyl alcohol of "inhibitory" components of the retinal action potential; their records showing diminished inhibition of the "off" discharge in the optic nerve by reillumination of the retina are less convincing.

Riggs (53) has made an ingenious contribution to the technique of recording retinal action potentials from human subjects. A small silver electrode was imbedded in the inner surface of a contact lens worn by the subject. This furnished a corneal lead free from disturbances due to eye movements and blinking. An artificial pupil was also incorporated in the contact lens.

Bishop & Bartley (54) have correlated features of the electrical responses of the anterior corpus quadrigeminum and the cortex of cats with the discharge of impulses in the optic nerve.

Olmsted & Morgan (55) photographed the Purkinje-Sansom reflection images from the eye of the rabbit, and also the profile of the lens, during stimulation of the cervical sympathetic nerve. They were able to show very clearly the flattening of the anterior surface of the lens that resulted.

#### HEARING

*Fluctuation of hearing.*—Near the threshold of hearing short sound stimuli of constant intensity are sometimes heard and sometimes not (56). This fluctuation has quite a different origin from that described in visual experiments (1). Lifshitz has computed that the intensity levels at which this effect was observed are too great to be accounted for by fluctuations in the physical stimulus caused by the ultimately statistical nature of pressure waves in air. The same effect could be detected at higher intensities. Short pulses of sound 6 db. above threshold appeared to fluctuate in duration, and to one observer, in loudness as well. Using flashes of light to mark the durations of the sound pulses, Lifshitz found (57) that the weak sounds appeared to begin later and later after the onset of the physical stimulus and to fluctuate in apparent duration more and more as the intensity of the sound was reduced toward threshold. These effects evidently must be ascribed to fluctuations in the sensitivity of the auditory system.

The ability to detect a change in the intensity or the frequency of a sound well above threshold also fluctuates. The greater the change, the more likely it is to be heard. Stevens, Morgan & Volkman (58) suggest that the neural processes causing these fluctua-



tions in differential sensory sensitivity may be described by "neural quanta" rather than in terms of random variation in sensitivity of the auditory mechanism. On this basis, a change in sensation is reported only when a sufficient number of "quanta" are brought into action (or dropped out). Data on intensity and frequency increments (1000 cycle note) revealed a linearity between size of the increment and percentage of presentations judged different, as required by the theory. The smallest increment that was always heard was very closely twice the size of the largest increment that was never heard, which, according to the theory, means that two "quanta" were required for discrimination. The size of the "quantum" was not constant but varied with the level of intensity and with other experimental conditions. It was found to be smaller when listening with two ears than when listening with one; this finding suggests its central location. The authors view this postulated "neural quantum" as a functional unit of the nervous system, involving a number of neurons.

*Frequency range of hearing in animals.*—The hearing of rats is poorer than that of man below 8 kc., but considerably better than that of man at higher frequencies (59). The maximum sensitivity of rats conditioned to respond to pure tones was found to be in the neighborhood of 20 kc. and was still quite high at 40 kc. The upper frequency limit of tones audible to the rats was probably still higher.

Top honors among the mammals, however, must go to the bat. Galambos (60, 61) has recorded cochlear potentials from bats in response to frequencies up to 98 kc. (limit of the apparatus, not of the bat!). The maximum voltage was obtained between 10 and 60 kc.; at 98 kc. the response was about one-third of what it was at 10 kc. Up to 55 kc. the intra-aural muscles were found to reduce transmission across the middle ear for high intensities. Normal flying bats emit supersonic cries (60) which they utilize, together with their ability to hear at high frequencies, to avoid obstacles (62). Bats which had been blinded showed no impairment of their skill in avoiding obstacles such as vertical wires, but either deafening them or gagging them to prevent them uttering their cries impaired their ability to the point where they hit such obstacles as frequently as was to be expected on the basis of chance. Bats with one ear deafened avoided large obstacles and could land normally, but could not localize the small wires. The authors have neatly solved



an old mystery: bats in flight emit supersonic cries and hear the echos reflected from obstacles, localizing them by binaural methods.

*Auditory fatigue.*—Holway, Staton & Zigler (63) have followed the recovery from auditory fatigue by determinations of threshold for a tone of 800 cycles presented at intervals after a 5 min. exposure to this same frequency. Several minutes may be required, depending on the intensity of the conditioning tone, for the threshold to return to the value it had prior to the exposure to the fatiguing tone. The authors explain their data in terms of lengthening of the "refractory periods" of the neurons in the auditory pathway as a result of the exposure, making fewer fibers available for hearing the threshold tone.

*Distortion.*—Wever, Bray & Laurence have conducted a series of investigations to determine the nature and the origin of the auditory distortion that produces overtones, combination tones, and interference. They analyzed with a wave analyzer the cochlear microphonics of the guinea pig. Comparisons were made of the responses to sound applied by the ordinary aerial pathway with the responses to driving the stapes directly—eliminating the middle ear. When two pure tones were presented together, the analysis showed that, in addition to the overtones of the two primaries, all the sum and difference combinations of them and of their integral multiples were present, up to high orders (64). The data could be satisfactorily accounted for quantitatively by the transformation theory that the combination tones are due to distortion in the ear. (A slight modification in mathematical detail was necessary.) The combination tones were present in the cochlear microphonics whether the sound reached the inner ear by the normal path or whether the stapes was driven directly (65). There was a noticeable difference which means that the middle ear may contribute to the distortion causing the combination tones. This contribution, however, was not great, and the general pattern of distortion, as revealed by measurement of overtones, combination tones, and interference, was not significantly altered by increasing the pressure in the middle ear cavity, provided the loss in sensitivity was compensated by increased intensity of stimulation (66). The middle ear, while not perfect, has a high degree of fidelity which it maintains even under conditions of stress imposed by pressure in its cavity.



Interference (67) is a new phenomenon revealed as a decrease in the magnitude of the cochlear microphonic response, measured at the frequency of the primary tone, as a result of the addition of a second tone. Interference is different from masking; it occurs between any pair of sounds whatever their frequency. It does depend on frequency, however, being closely (but not exactly) related to the sensitivity of the ear at the various frequencies. The loss due to interference is in a large measure accounted for by the diversion of energy of the fundamentals into the production of combination tones. It thus has its origin in auditory distortion. In the experiments reported, interference could be obtained if the interfering tone was supplied by bone conduction, or if both tones were applied directly to the stapes. It is therefore due to the action of the inner ear. After injury to the spiral organ (of Corti) by overstimulation the interference produced by a given tone was less, even though compensation for the lowered level of responses to the primary tone was made (68). The authors believe that this distortion has its origin in the hair cells of the spiral organ.

*Electrophonics.*—Sound sensations can be elicited by the application of alternating electric current to the ear. Jones, Stevens & Lurie (69) investigated this electrophonic effect in patients whose ears had been operated upon and lacked ear drum and ossicles. Normal ears hear a tone an octave higher than the applied frequency, unless a direct current polarizing potential is applied, in which case they hear the fundamental as well. This is due to electrostatic attraction of the ear drum by the opposite wall of the middle ear. Most of the patients who lack an ear drum also heard tones when alternating current was applied, but they heard pure tones corresponding in frequency with the applied electrical stimulus. This "linear" hearing must arise in the inner ear and is thought by the authors to be due to the inverse of the cochlear microphonic effect. A pure tone was heard because a particular frequency of alternating current produced resonant vibrations of that part of the basilar membrane normally driven by sound waves of the same frequency. Some of the operated patients also heard a buzzing noise whose character was independent of frequency. This was ascribed to stimulation of fibers of the auditory nerve. These findings are taken as evidence against the "telephone" theory of hearing, and in favor of the "place" theory.

*Additional studies on hearing.*—Evidence that the classical



ideas concerning the function of the round window must be modified is presented by Hallpike & Scott (70). Experimental occlusion of the round window produced no change in sensitivity to sound in cats, as determined by action potentials from the auditory tract. (Contrary results of Hughson & Crowe (71) are ascribed by the present authors to electrical artifacts in the recording of cochlear potentials.) No gross loss of hearing was detected in one human subject whose round window was occluded by bone. The authors suggest that frictional losses in the cochlea may take the place of the assumed mobility of the round window in the theory of hearing.

Grüneberg, Hallpike & Ledoux (72) report their findings on a strain of white mice which showed normal postfetal development of the internal ear, completed twelve days after birth, but which shortly afterwards (38 days) developed deafness and concurrently showed diminished cochlear potentials and exhibited pathological changes in the scala media. The changes appeared first in the stria vascularis and the spiral organ (of Corti) and were progressive. Presumably the spiral organ is functionally dependent on the supply of endolymph by the stria. The failure of cochlear potentials simultaneously with damage to the spiral organ would appear to support the view that the cochlear microphonics originate in the latter. However, the authors do not accept this explanation, arguing that Reisner's membrane, which they believe is responsible for the cochlear potentials, may also be functionally impaired as a consequence of changes in the stria vascularis.

Davis (73) presents a brief review in which he discusses recent developments in the physiology of hearing. The role of the intraural muscles and investigations on bone conduction are discussed. He points out that it is now possible to construct a map of the basilar membrane consistent with six independent sets of data: (i) position of maximum electrical activity of the cochlea; (ii) impairment of electrical activity of the cochlea by localized lesions; (iii) pathological changes associated with high-tone deafness; (iv) integration of just-noticeable differences in pitch; (v) contributions of different parts of the basilar membrane to the total loudness of a sound; (vi) relation of pitch, subjectively perceived, to frequency. He concludes a discussion of electrophonic effects, including the work of Jones *et al.* (69), discussed above, with the remark that the analyzing mechanism of the inner ear remains an essential part of the mechanism of hearing.



## VESTIBULAR MECHANISM

The mechanism of the semicircular canals has been elegantly clarified by two papers of Löwenstein & Sand (74, 75). Recording the electrical activity in single fibers of the ampullary twigs of the vestibular nerve from the excised labyrinth of the ray, the authors were able to demonstrate the responses to rotation of the hair cells in the sensory crests of the ampullae. When the preparation was at rest, these receptors were in a state of tonic activity, producing a steady discharge of impulses. Rotation in one direction gave rise to an increased frequency of discharge; in the opposite direction it diminished the frequency. The horizontal canals responded to rotation about a vertical axis; excitation (increased frequency) occurred when the rotation was in such direction that the ampulla of the canal trailed. The vertical canals were excited by rotation with the ampulla leading; they responded to rotation about any axis. The threshold at which an effect on the discharge could be detected was an angular acceleration of  $3^\circ$  per sec. per sec. During the uniform angular acceleration the frequency increased or decreased gradually, in a linear manner, its rate of change being proportional to the acceleration. During prolonged rotation at a constant speed the frequency of discharge, having passed through a maximum or minimum because of the initial acceleration, gradually returned to its original spontaneous value in about twenty seconds. These results can all be interpreted in accordance with Steinhausen's findings (76) on the physical properties of the canal and the gelatinous cupula which overlies the sensory crest in the ampulla. The basis for the interpretation of reflex responses to rotation is found in these properties of the individual canals and in the way all six canals work together. The authors have described the synergic actions of the canals as a result of rotation about the various axes and have shown how these simple sensory properties can explain the eye muscle reflexes. While many of these properties of the semicircular canals have already been deduced from classical experiments, the substitution of direct observation for inference and deduction is especially gratifying in this field.

## TASTE

Pfaffmann (77) has made a direct analysis of gustatory function in the cat by recording the activity in single fibers from the chorda tympani or from the glossopharyngeal nerve. Responses were elic-



ited by solutions of various substances placed on the tongue. He found three different types of gustatory fibers which discharged impulses: (a) those which responded to acid only, (b) those which responded to both acid and salt (sodium chloride), and (c) those which responded to both acid and quinine. Adaptation of the gustatory receptors was slow; both the initial and the final level of frequency depended on the concentration of the stimulating substance. The different fibers were not exclusively sensitive to the chemical by which they were identified; for each fiber type there was a group of chemicals to which that type was sensitive. A fiber responding to two different chemicals, acid and salt, or acid and quinine, showed in its discharge nothing which was characteristic of the particular chemical employed. No differences could be detected in rate of adaptation or in grouping of impulses which could serve to distinguish the different chemicals which could excite such a fiber. This is significant, for it is direct evidence that a single fiber does not discriminate different kinds of stimuli by any sort of "modulation" of its discharge. Qualitative discrimination must be accomplished by the sense organ as a whole, comprised of receptors which are differentially sensitive. Different kinds of stimuli thereby set up characteristic patterns of activity among the fibers of the sensory nerve trunk.

#### CUTANEOUS SENSES

The literature on pain and temperature has recently been reviewed by Stone & Jenkins (78). A review of the physiology of itching by Rothman (79) presents the view that itching is identical in quality with protopathic pain and is mediated by C fibers. Episcritic stimulation can depress this sensation, and its removal results in accentuation of itching. He discusses the evidence that the fibers involved constitute a ramifying axon system in the skin, mediating diffuse effects because of axon reflexes. Wolf & Hardy (80) studied the deep aching pain induced by immersing the hand in cold water. This pain was distinct from the sensation of cold, although the local temperature gradients were responsible for eliciting it. It did not exhibit spatial summation. From the results of selective partial nerve block it was suggested that this pain was mediated by C fibers. Jenkins (81), in continuing his work on the temperature sense, reported that, once the threshold to warmth of a given small area was reached, further increase in stimulus tem-



perature gave rise to no stronger sensation; this led the author to suggest an "all-or-none" response of the receptors involved. No sensory receptor is known which shows, upon direct observation, this manner of response. Temperature receptors, however, have not yet been studied in detail by electrophysiological methods.

A worthy contribution to the physiology of cutaneous receptors has been furnished by Fitzgerald's study (82) of the tactile receptors of the cat's vibrissae. He has recorded the discharges of nerve impulses in single fibers from these receptors produced by bending or exerting traction upon the hair. The responses of the receptors of ordinary hairs cease completely after the discharge of a very few impulses, but the discharges from these receptors of the vibrissae in response to a steady displacement of the hair can last as long as ten minutes. Fitzgerald found that the potassium ion caused spontaneous activity and resulted in stronger responses to stimuli. This was followed by depression of responses if the concentration of potassium ions was high enough. It seems unlikely, therefore, that the potassium ion is the agent responsible for adaptation of an end organ. Calcium ions antagonized the potassium ion effect, and by itself served to diminish the frequency of discharge in response to a given stimulus and to speed up the adaptation of the receptor.

#### VISCERAL AFFERENTS

The functions of the carotid and aortic bodies in the control of circulation and respiration have been thoroughly reviewed by Schmidt & Comroe (83). Highly vascularized and richly innervated epithelioid bodies in the abdomen of the mouse have been described by Hollingshead (84). They are apparently chemoreceptors similar to those in the carotid bodies.

Knowlton & Larrabee (85) recorded the activity in single afferent fibers from the lungs. They demonstrated the presence of rapidly adapting stretch receptors and distinguished them from the slowly adapting kind already known. Some of both kinds of receptors responded to forced deflation as well as to inflation of the lungs. These receptors account for the afferent mechanism of known respiratory reflexes.



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THE ELDRIDGE REEVES JOHNSON RESEARCH FOUNDATION  
UNIVERSITY OF PENNSYLVANIA  
PHILADELPHIA, PENNSYLVANIA



## METABOLIC FUNCTIONS OF THE ENDOCRINE GLANDS

BY C. N. H. LONG<sup>1</sup>

*Department of Physiological Chemistry,  
Yale University School of Medicine,  
New Haven, Connecticut*

In writing the present review the author has selected a number of topics from papers largely published during the period August, 1940, to September, 1941. They have been chosen not only on account of their personal interest to the reviewer but also because they appear to reflect the major trends of work in the subject under discussion.

It will be noted that the bibliography consists almost entirely of papers published in the English language. This, in part, is due to the unavailability of many foreign journals but in many instances, even when the journals were consulted, it was found that little work of any significance in this field has appeared in foreign periodicals in the period under review.

### THE ANTERIOR PITUITARY

The diversity of metabolic changes induced by the injection of anterior pituitary extracts continues to make an orderly understanding of the function of this gland exceedingly difficult. This is in part due to the different types of extracts used by investigators. A crude extract contains not only principles that act directly on the tissues but also those that exert their effects on metabolism by stimulation of the adrenal cortex and thyroid, and variations in the preparation of the extract may result in the presence of different proportions of the hormones in the final product used. Thus, the conflicting reports on the effect of pituitary extract on liver glycogen content might be due to the relative quantities of adrenotropic, thyrotropic or other factors present in the extract. An excess of adrenotropic extract would probably increase the liver glycogen (1), while it may be presumed that the administration of a preparation rich in the thyrotropic hormone

<sup>1</sup> I am indebted to Mr. D. W. Seldin for assistance in the compilation of the material used in this review.



would ultimately cause a decrease. It is apparent that a satisfactory solution of the number of metabolic hormones present in this gland as well as a definition of their particular activity must rest on their isolation in pure form. During the past year several papers dealing with the isolation of various factors with an influence on metabolism have appeared.

#### PURIFICATION OF ANTERIOR PITUITARY METABOLIC HORMONES

Two recent papers outline methods by which a crude anterior pituitary extract may be divided into a number of components in which one particular type of activity is present in excess. Bonsnes & White (2) describe a procedure by which 2 per cent saline extract of beef anterior lobes may be fractionated into protein fractions. From these, evidence was obtained for the presence of four distinct chemical entities with different biological activities. These were lactogenic, thyrotropic, and adrenotropic fractions, and one that was not only growth promoting but in addition possessed diabetogenic and ketogenic activity. The increase in potency of the last fraction as compared to the original was not particularly marked. More recently Ciereszko & White (3) state that treatment of the saline extract with lead acetate, followed by removal of the lead with phosphate, divided the activities into two parts. The supernatant solution contained only 15 to 20 per cent of the original nitrogen content of the extract but retained practically all of the original thyrotropic, adrenotropic, and gondotropic activity, and only slight amounts of growth-promoting and lactogenic hormone. Fevold *et al.* (4) simultaneously reported the separation of an alkaline extract of whole sheep pituitaries into five different protein fractions in which either growth-promoting, lactogenic, thyrotropic, luteinizing, or follicle-stimulating activity was predominant. They report significant increases in the concentrations of hormones present as compared with the original extract, particularly in the case of the growth-promoting activity.

Fraenkel-Conrat and his collaborators (5) describe an extraction method by which a preparation rich in growth-promoting activity and containing only small amounts of the other hormones may be obtained. This purification is effected largely by treatment with cysteine which inactivates the gonadotropic and thyrotropic hormones without affecting the growth activity.



The lactogenic principle although not inactivated is precipitated by this reagent if the right conditions are observed. Treatment with cysteine did not destroy the ability of this preparation to lower the respiratory quotient and produce ketosis in rats. The close association of these last two effects with the growth-promoting activity has been frequently noted. The authors emphasize that the growth-promoting activity of the anterior pituitary cannot be attributed to a synergistic activity of other pituitary principles but must be due to a separate entity.

Bates, Riddle & Miller (6) describe a new method for the preparation of adrenotropic extracts. Their work indicates that they have succeeded in obtaining this principle in a greater concentration than heretofore achieved and that the preparation is essentially free from other pituitary factors.

Considerable progress has also been made in the purification of the thyrotropic hormone. Fraenkel-Conrat *et al.* (7) have obtained a hundredfold concentration with the loss of only one third of the activity in the starting material. The initial extraction of the beef anterior pituitaries was with slightly acid sodium chloride solution (1 per cent) following which the solution was treated with acetone to a concentration of 50 per cent. From this supernatant fluid repeated fractional precipitation with ammonium sulfate yielded a product in which one chick unit was equivalent to 1.6 to 3.5  $\mu$ g. of nitrogen. The product was practically free of growth, lactogenic, and gonadotropic hormones. The protein character of the hormone was indicated by the empirical analysis. Jorgensen & Wade (8) state that sheep pituitaries are a poor source of thyrotropic hormone in comparison to beef glands. They also report considerable purification of the hormone by differential adsorption on permutit at pH 4.5. Subsequent concentration by precipitation with uranium acetate yielded a product free from growth or gonadotropic activity. Although the activity was followed by the chick method the data in this paper do not permit a direct comparison of the potency of this product with that of Fraenkel-Conrat *et al.*

Ciereszko & White (9) found the thyrotropic principle to be present in the material precipitated by 75 per cent acetone at pH 4.0 from a saline extract of beef glands after the previous removal of fractions at pH 5.5, 4.9, 4.0. Further concentration could be achieved by extraction of the dried precipitate with



water and treatment of the water solution with lead acetate. Further fractionation with acetone and trichloroacetic acid yielded a product containing 17.5 per cent nitrogen in which 1 chick unit was equivalent to 0.2  $\mu$ g. of nitrogen (private communication). It should be noted, however, that Fraenkel-Conrat *et al.*, used the amount of nitrogen required to produce a 33 per cent increase in the weight of the chick thyroid as their unit while Ciereszko & White used the amount required to produce a minimal histological response. None of these groups of investigators report the activity of their preparations in terms of their ability to increase the basal metabolic rate.

While considerable progress has been made in the purification of the growth, adrenotropic, and thyrotropic hormones, as well as in that of the lactogenic and gonadotropic factors, the concentration or isolation of other metabolic principles has been less successful. This may be due in part to the nonexistence of several that have in the past been designated as separate hormones. Among those concerning which there is still uncertainty are the ketogenic (production of ketosis in fasting animals), the fat metabolism (production of fatty liver), the glycostatic (maintenance of muscle glycogen levels of hypophysectomized animals), glycotropic (resistance to insulin), which is probably identical with the adrenotropic, diabetogenic (production of hyperglycemia and glycosuria), and R.Q. depressing factors. In addition, Collip and his collaborators have described a specific metabolic principle which is distinguished by possessing glycostatic, ketogenic, and R.Q. depressing properties as well as the ability to increase the total metabolism. Neufeld & Collip (10) now report that they have prepared from both anterior and posterior lobes protein hydrochlorides that increase the body glycogen content of mice. These powders, although not possessing thyrotropic, gonadotropic, or growth-promoting properties, did, in the case of the anterior lobe preparation, contain some adrenotropic and diabetogenic activity and a marked degree of lactogenic activity. Feinstein & Gordon (11) state that although the response of the basal metabolic rate and depression of the R.Q. after the injection of extracts prepared by Collip's method into men and rabbits is erratic, they believe that their data support the conclusion that the pituitary contains a specific metabolic principle. Campbell & Keenan (12) describe a method for the preparation from fresh beef anterior lobes of extracts that



are effective in increasing the liver fat of mice. They find that the agent responsible is not necessarily associated with prolactin, ketogenic, or melanophore-expanding activity.

It is extremely difficult at the present time to make any positive statements as to how many separate metabolic factors are present in the pituitary. It is, however, the opinion of this reviewer that further work, particularly on the chemistry of these extracts, will reduce rather than increase the number of metabolic hormones.

#### THE INFLUENCE OF THE ANTERIOR PITUITARY ON CARBOHYDRATE AND PROTEIN METABOLISM

The papers that have been published during the past year have been extremely revealing in the light they have thrown on the manner in which the anterior pituitary regulates certain phases of carbohydrate and protein metabolism. Furthermore, they have emphasized the difficulty of attempting to segregate the effect of any individual endocrine gland without consideration of the balanced and reciprocal action that exists between the several members whose secretions are necessary for a normal metabolism.

For convenience of discussion, the papers fall into three groups: (a) those dealing with the influence of the anterior pituitary and variation in the composition of the diet on the insulin content of the pancreas, (b) those in which studies have been made of the metabolism of animals rendered diabetic by anterior pituitary injections, and (c) those that report work on the mechanism and site of action of anterior pituitary hormones on carbohydrate and protein metabolism.

*The anterior pituitary and the insulin content of the pancreas.*—Best and his colleagues (13) have previously shown that the insulin content of the rat pancreas may be determined by pooling the organs obtained from groups of ten to twenty animals. The insulin content of the pancreases of their animals when fed a mixed diet was about 0.7 to 0.9 units per 100 gm. of body weight. Fasting or feeding of high fat diets reduced it to about half the original value while a diet of carbohydrate alone caused only a slight reduction. After a fast the feeding of fat did not bring about an increase in the insulin content while carbohydrate alone caused a partial restoration. They suggested that the insulin content is directly related to the rate of insulin liberation. Finally, Best & Haist (14) have recently reported that the daily injection of protamine zinc



insulin into fed rats brings about a striking reduction in the insulin content of the pancreas which is even greater if the animals are fed a fat diet. Similar injections into fasting rats produced a greater fall in insulin content than fasting alone. This technique has since been applied to a number of circumstances in which the rate of insulin production is an important factor in the interpretation of the observed results.

The most interesting of these is the question of the control of insulin secretion by a "pancreatotropic" hormone of the anterior pituitary. The suggestion that such a hormone exists came from the studies some years ago of Anselmino & Hoffmann, who claimed that the injection of certain anterior pituitary fractions into rats was followed by hypertrophy of the islands of Langerhans. The occurrence of such hypertrophy was confirmed by Richardson & Young (15) who, however, failed to substantiate the claim that a particular pituitary fraction was concerned since in their experiments the greatest effects were obtained after treatment of the animals for some days with a crude saline extract. Following the observation of Young that permanent diabetes could be produced in dogs by injection of such extracts and that this was associated with islet destruction, Best, Campbell & Haist (16) have shown that this treatment drastically lowers the insulin content of the dog pancreas within a few days after starting the injections. If treatment were then stopped the insulin content slowly returned to normal but if continued until permanent diabetes was established no recovery of insulin content could be obtained, and there is good reason to believe that the diabetes continued by reason of the almost complete destruction of the insulin-secreting cells. However, as Lukens & Dohan (17) have recently shown in the cat the diabetes may be allowed to continue for several weeks and then if the animals are adequately treated with insulin for a few weeks the subsequent withdrawal of insulin is not followed by glycosuria. Indeed, the animals may be said to have recovered from the diabetes and this conclusion was borne out by histological examination of the islands which showed that the characteristic hydropic degeneration present prior to insulin treatment had disappeared.

However, while these experiments indicate that anterior pituitary extracts are capable of decreasing insulin production, the question as to whether they first exert a stimulatory action is not



answered by them. In the rat, Marks & Young (18) found that the daily administration of crude anterior pituitary extract doubled the insulin content of the pancreas. Such an increase even in the early stages of treatment has not been observed in the dog but may be in keeping with the very different susceptibility of these two species to the "diabetogenic" action of the anterior pituitary: the rat is very resistant and permanent diabetes has not yet been produced by pituitary extracts in this species. Marks & Young noted that the pancreatotrophic action accompanied the growth-promoting and diabetogenic action and in another paper (19) they report that the activity is not associated with the thyrotropic or gonadotropic properties of the extracts. They suggest that there is no conclusive evidence for the existence of a separate factor that brings about hypertrophy and increased insulin content of the pancreas.

The view that the influence of the anterior pituitary upon the islands of Langerhans is an indirect one is supported by another related line of evidence. In the case of all other endocrine glands whose activity is governed by a "tropic" hormone, the removal of the pituitary is followed by their atrophy and other evidences of hypofunction. Now it is quite evident that hypophysectomized animals do not exhibit any signs of insulin deficiency. On the contrary many of their reactions suggest an abnormally high ability to utilize carbohydrate. Furthermore, there is no histological evidence to suggest that the islands are not normal in hypophysectomized animals. Bakay (20) found that in dogs two to six months after hypophysectomy the islands were increased both in size and number and showed evidence of increased secretory activity. Indeed, he concludes that the pituitary secretes an anti-islet hormone.

Apart from the morphological evidence, Haist (21) has shown that hypophysectomy only slightly reduces the insulin content of the pancreas of rats and as in the case of intact animals fat feeding brings about a fall. If the rats were then placed on a balanced diet, the insulin content returned to normal in about a week. Griffiths (22) has also shown that hypophysectomy does not alter the insulin content of rats and that when the operated animals are injected with growth-promoting extracts the increased body weight is accompanied by an increase in pancreatic insulin. Soong (23) has reported similar experiments. He also finds little, if any, effect of



hypophysectomy and reports that the administration of anterior pituitary extract is followed both in normal and hypophysectomized rats by an increased insulin content. Evidently the capacity of the islet tissue to form insulin is not only unaffected by removal of the pituitary, but it is still able to respond to variations in the demand for insulin by the tissues.

However, in a recent short communication, Funk *et al.* (24) state that alkaline anterior pituitary extracts can be divided into two fractions, one of which increases while the other decreases the insulin content of rat pancreas. The magnitude of the fall in insulin content was not particularly striking although there would seem to be no doubt that they obtained an increased insulin content after giving a "globulin like" fraction. On the other hand, they make the surprising claim that the injection of purified prolactin brought about a virtual disappearance of insulin in three of the four preparations tested. Since this hormone has never been shown to be a "diabetogenic" agent it is difficult to understand why it should so drastically lower the insulin content.

There are also reports to suggest that the anterior pituitary hormones are not the only ones that may cause alterations in the insulin content of the pancreas. Griffiths, Marks & Young (25) found, following the implantation of tablets of diethyl stilbestrol, estriol, and estradiol into rats, that the insulin content of the pancreas was increased. Cholesterol, estrone, and testosterone were inactive. Funk *et al.* also state that stilbestrol and estradiol increase the insulin content and that progesterone and testosterone cause a small decrease. It should be noted that stilbestrol will produce glycosuria in normal rats (26) while it is stated that the estrogens will aggravate the glycosuria of partially depancreatized ferrets (27).

The marked effects of certain adrenal steroids on carbohydrate metabolism are discussed elsewhere. Haist & Best (28) report that adrenalectomy did not alter the insulin content of rats given a balanced diet and maintained with sodium chloride. The administration of a high fat diet led to a fall in insulin content but when 3 to 6 cc. of cortical extract was given by mouth to adrenalectomized rats on a balanced diet no change could be detected in the insulin content of the pancreas. However, since 11-dehydro-17-hydroxycorticosterone will produce glycosuria in normal rats (26), it would be well to reserve judgement on the influence of adrenal



steroids of this type since the quantities of extract given in these experiments may not have been sufficient to produce detectable effects.

The present evidence would indicate that the production of insulin is not directly dependent on endocrine factors. It seems entirely probable that the demands of the organism expressed through the level of the blood glucose are the factors that regulate insulin production and supply. Circumstances that depress the general level of blood glucose lessen the requirements for insulin while those that result in an elevation of blood glucose stimulate an increased insulin production. A continued stimulation such as is produced by a continued high level of blood glucose appears to bring about, at least in some species, an ultimate failure of the insulin secretory mechanism.

The apparent importance of the blood glucose level is illustrated by the experiments of Lunkens & Dohan (29). As mentioned above these investigators had previously shown that insulin treatment of cats with a permanent diabetes induced by anterior pituitary extract was followed by morphological and functional recovery of the pancreatic islands. They now find that phlorhizin injections, which markedly lower the blood glucose of these animals, are followed by recovery as judged by the subsequent absence of glycosuria and a normal blood glucose level.

*The metabolism of dogs with pituitary diabetes.*—Dohan & his collaborators in two papers (30, 31) have reported on the metabolism of dogs rendered permanently diabetic by the injection of pituitary extract. These papers along with that of Marks & Young (32) have now given us a fairly complete picture of the metabolic characteristics of these animals. They are too long to be reviewed here in detail, but both groups of investigators are agreed that with certain exceptions the metabolism of these dogs closely resembles that of depancreatized animals and that the alterations observed can be best explained by loss of function of the islands of Langerhans.

*The mechanism and site of action of anterior pituitary metabolic hormones.*—The injection of anterior pituitary extracts affects the metabolism of all classes of foodstuffs. Thus their injection may be followed by hyperglycemia (and glycosuria), ketosis, and increased quantity of liver fat, and a retention of nitrogen. In the latter case if the injections are long continued and diabetes occurs,



the nitrogen retention may ultimately be replaced by an increased loss of this element in the urine. Two questions have arisen from these observations (*a*) what is the mechanism and site of action of anterior pituitary extract and (*b*) how many pituitary hormones are involved? This last question has already been discussed and a final answer seems unlikely until the purification of extracts has progressed beyond its present stage.

The changes in metabolism cited above are those associated with the diabetic state and since the nature of the fundamental disturbance in this condition is still the subject of some difference of opinion it is inevitable that the contending views expressed would also be offered in explanation of the mechanism of action of the anterior pituitary. Briefly, these two opposing views are (*a*) that the anterior pituitary depresses the peripheral utilization of glucose and in addition either directly or indirectly stimulates glucose production in the liver from protein, and (*b*) that the site of action of the anterior pituitary hormones is largely, if not entirely, confined to the liver where it stimulates glucose production not only from protein but also from fatty acids. Furthermore, it is held that it does not influence glucose utilization in the peripheral tissues. Last year in these reviews Soskin (33), who is one of the leading protagonists of the second point of view, presented his interpretation of the known facts. Since this group is unwilling to accept evidence for an alteration in glucose utilization based on respiratory data, it is interesting to note that two papers have recently appeared that demonstrate by direct methods that removal of the pituitary increases the capacity of the peripheral tissues to utilize, if not oxidize, glucose and that the administration of pituitary extract prevents the loss of muscle glycogen observed in hypophysectomized rats. Greeley (34) has reported that the intravenous utilization of glucose is abnormally high in hypophysectomized rabbits and that the sugar disappearing could not be accounted for by deposition as liver glycogen or transformation into fat. Furthermore, removal of the liver and intestinal tract did not alter this high rate of utilization. Russell (35) has shown that not only was the survival period of eviscerated rats reduced by hypophysectomy (but not adrenalectomy), but the muscle glycogen levels, that remain constant in normal eviscerated animals provided the adrenal medullae have previously been removed, fell rapidly. The injection of anterior pituitary extract, and to a



lesser degree adrenal cortical extract, not only prolonged the survival time but also prevented the fall in muscle glycogen. The intravenous utilization rate of glucose was found to be approximately 13.5 mg. per 100 gm. an hour in the normal animals after evisceration and about 25 mg. per hour after hypophysectomy. In addition, the rate of fall of blood glucose after cessation of the glucose infusion was three times as fast in the hypophysectomized group. These two papers would appear to have demonstrated that the anterior pituitary does exert an effect on the peripheral utilization of glucose. This, of course, does not exclude the occurrence of an effect on the liver and there is good reason to believe that the adrenotropic hormone may act on this organ to increase glucose formation from protein. The question as to whether fatty acids may be converted into glucose under any circumstances has recently been examined with a negative conclusion by Stadie *et al.* (36).

The influence of the anterior pituitary on protein metabolism is closely associated with the ability of extracts of this organ to promote growth in animals. It has been known for sometime that the injection of extracts rich in growth-promoting properties into normal animals is followed by a decreased nitrogen excretion. The question as to whether this retention of nitrogen is mediated by the stimulating effects of the extract on insulin secretion has been studied by Gaebler & Galbraith (37) who injected such extracts into depancreatized dogs maintained under constant conditions of diet and insulin. The extracts, which had previously been shown to cause nitrogen retention in normal animals, produced marked glycosuria and an increased nitrogen excretion in the diabetic animals. Even in this case, however, the glycosuria was much increased by the pituitary injection. Gaebler & Galbraith conclude that an increased insulin output is not the immediate and only cause of the nitrogen retention although the presence of sufficient insulin may be an essential condition for it to occur. Paschkis (38) has shown that pituitary extracts reduce the blood urea nitrogen of normal, adrenalectomized, and partially depancreatized fasted rats and states that this change is independent of any change in blood glucose. He concludes that the anterior pituitary acts independently on the protein and carbohydrate metabolism, a conclusion that may also be read into the results of Gaebler & Galbraith. In a previous paper (39) Paschkis suggested that the



effects of the anterior pituitary extract on growth and nitrogen retention are due to two separate entities. His evidence for this, which is based on the normal response of the blood amino acid nitrogen of two pituitary dwarfs after gelatin feeding, is not very convincing and it seems logical to assume that the growth-promoting properties of pituitary extracts are due to their influence on protein anabolism. At any rate their ability to decrease nitrogen excretion has been shown not only in fed but also in fasted and phlorhizinized animals (40, 41).

It is evident that the ability of an animal to grow is not dependent on a single pituitary principle and, indeed, as Salmon (42, 43) has shown rats thyroidectomized at birth do not respond to the growth-promoting activity of anterior pituitary extracts. It is probable that other hormonal, vitamin, and mineral deficiencies will be shown to inhibit the growth-promoting action of the anterior pituitary, although it may still induce a temporary nitrogen retention.

Freud and his collaborators (44) have reviewed their studies on the influence of growth-promoting extracts on the proliferating zone of cartilage. Although at first inclined to the view that the hormone acted specifically on this tissue they now state (45) that the hormone also has a general systemic effect. Ross & McLean (46) find that not only is the cartilage stimulated, even though in a quiescent state, but that the adjacent spongiosa is also involved. They note that the influence on these tissues of the preparations used was a better indication of activity than the increase in body weight. They also record their belief that these alterations in cartilage and bone do not exclude specific effects of the growth-promoting hormone elsewhere in the body.

## THE ADRENAL CORTEX

### THE INFLUENCE OF THE CORTICAL HORMONES AND OTHER STEROIDS ON CARBOHYDRATE AND PROTEIN METABOLISM

A considerable number of papers have appeared during the past year that emphasize the important role of the adrenal cortex in the regulation of certain phases of carbohydrate and protein metabolism. While there is still a difference of opinion as to the exact effects of this hormone, the marked divergence in the point of view of various investigators that existed some years ago has



disappeared since it is now recognized that this endocrine gland exerts positive effects on both the organic and inorganic metabolism. Indeed, at the present time the effects of certain steroids derived from the adrenal cortex on carbohydrate metabolism seem to be more specific than their influence on electrolyte metabolism.

In previous work it has been shown that the cortical hormones are essential for a normal rate of gluconeogenesis from protein (47). Thus, under circumstances in which an increased rate of gluconeogenesis constitutes part of the response of the organism, it has been found that the adrenalectomized animal shows noteworthy deficiencies. Among conditions of this kind that have been examined are fasting, phlorhizin diabetes, pancreatic diabetes, and exposure to low oxygen pressures. It is also important to note that not all the steroid hormones isolated from the adrenal cortex and other sources are equally active in restoring a normal rate of gluconeogenesis. In a series of papers Kendall and his colleagues have found marked differences in the ability of adrenal steroids to maintain the glycosuria and ketonuria of fasted rats. Those that contain an hydroxyl or ketone group at carbon 11, such as corticosterone, 11-dehydrocorticosterone, and 11-dehydro-17-hydroxycorticosterone, are effective while 11-desoxycorticosterone or the amorphous fraction of cortical extracts that remains after removal of the crystalline compounds are practically inactive. A similar result was obtained by Long, Katzin & Fry using the adrenalectomized, partially depancreatized rat.

Thorn and his colleagues (48) have studied in patients with Addison's disease the relative ability of these two types of adrenal steroids to repair the defects in carbohydrate metabolism. Their results give an unusually complete confirmation of the animal experiments. By the use of a standard intravenous glucose tolerance test coupled with determinations of the respiratory exchange and nitrogen excretion they found that a high proportion of individuals with Addison's disease had a disturbed carbohydrate metabolism. This included: (a) subnormal fasting blood glucose, (b) an evident hypoglycemia following glucose infusion or ingestion, (c) a flat type of oral glucose tolerance curve, (d) unusual occurrence of hypoglycemia symptoms associated with the abnormal depression of the blood glucose after glucose ingestion, and (e) a high fasting respiratory quotient which rose to levels above normal after glucose administration.



Treatment with desoxycorticosterone acetate (30 mg.) did not correct any of these abnormalities with the exception of the shape of the oral glucose tolerance curve. On the other hand, the administration of cortical extract (50 cc.), corticosterone (85 mg.), or 11-dehydro-17-hydroxycorticosterone (33 mg.) restored the carbohydrate metabolism to normal and in addition produced a significant augmentation of nitrogen excretion. The injection of 11-dehydro-17-hydroxycorticosterone also produced glycosuria during the glucose tolerance test.

Ingle & Thorn (49) have also tested the comparative effect of 11-desoxycorticosterone acetate and 11-dehydro-17-hydroxycorticosterone in partially depancreatized rats both with or without their adrenals. Animals chosen for the test were not excreting glucose under the dietary conditions employed (daily tube feeding of a fluid diet). They observed very striking differences. The injection of 1, 2, or 5 mg. a day of the 11-dehydro-17-hydroxy compound was followed by profuse glycosuria, ketonuria, and an increased excretion of nitrogen, phosphorus, and potassium. The animals lost weight rapidly and ultimately died from what appeared to be diabetic acidosis. Treatment with equivalent quantities of desoxycorticosterone did not produce any marked changes except a slight increase in potassium excretion. The injection of larger quantities (10 mg. a day) was followed by a mild degree of glycosuria in two out of five animals. Another difference between these two substances was their effect on the sodium chloride excretion. Desoxycorticosterone produced sodium chloride retention in eleven out of twelve rats at dose levels of 1 to 5 mg. daily while equivalent amounts of 11-dehydro-17-hydroxycorticosterone produced some retention in a few rats, but more frequently increased the sodium chloride excretion. It should also be noted that the increased glycosuria after 11-dehydro-17-hydroxycorticosterone could not be entirely accounted for in terms of the increased protein catabolism, indicating that this hormone also inhibited carbohydrate utilization.

Even more interesting is the recent announcement by Ingle (26) that 11-dehydro-17-hydroxycorticosterone in doses of 5 to 10 mg. a day would induce hyperglycemia and glycosuria in normal rats. One of the animals so treated succumbed. As in the experiments with partially depancreatized animals the increased nitrogen excretion was insufficient to account for the observed glycosuria.



From this work and that of others there is now no doubt that this substance is a powerful "diabetogenic" agent.

In the same paper Ingle also reports that the synthetic estrogen stilbestrol, in quantities as small as 50  $\mu$ g. a day, would produce hyperglycemia and glycosuria in two thirds of the rats studied. However, adaptation to these injections usually occurred in periods of from two to thirty-six days and the "diabetogenic" action did not appear to be as intense as with the cortical hormone.

Dolin, Joseph & Gaunt (27) have used the partially depancreatized ferret as a test object for "diabetogenic" substances. They report that as in other species the injection of anterior pituitary extract or cortical extract augments the glycosuria. 11-Desoxycorticosterone and progesterone were inactive but naturally occurring estrogens had a positive effect. They suggest that the effect of the latter may be due to the adrenal cortical hyperplasia they are known to produce.

Corey (50) has found that progesterone injections in amounts of 1 to 5 mg. a day into fasting adrenalectomized or hypophysectomized rats had no effect on the carbohydrate levels although this hormone did prolong the survival period of adrenalectomized cats. Britton & Kline (51) have compared the activity of 11-desoxycorticosterone with that of whole cortical extracts in their ability to sustain the life of adrenalectomized cats as well as their carbohydrate levels. They find that desoxycorticosterone will slowly restore the animals to normal (six to twenty-four hours) provided the degree of insufficiency is not too severe, in which case it is ineffective. If the animals responded to the treatment, the electrolyte and carbohydrate levels gradually returned to normal. Cortical extract acted much more rapidly on these levels and in addition soon restored moribund animals to normal. Similar results were observed in adrenalectomized rats. They conclude that while desoxycorticosterone given in moderate doses will maintain a normal carbohydrate metabolism in adrenalectomized animals it has, in all probability, no direct influence on carbohydrate metabolism. They regard its action as mainly upon the water and electrolyte metabolism.

Hartman and his colleagues (52) have separated cortical extract into two fractions, one which influences the sodium balance of the organism (sodium factor) and another which is essential for the maintenance of life in adrenalectomized animals (cortin). Both



fractions apparently have some influence on carbohydrate metabolism since they increase the liver glycogen of fasted mice and decrease insulin convulsions. The cortin factor, however, is the more active (53). Selye (54) has found that  $\Delta^5$  3-hydroxy-21-acetoxypregnene-20-one or acetoxypregnenolone, an intermediary product in the Steiger and Reichstein synthesis of desoxycorticosterone, is capable of maintaining the life of adrenalectomized rats. This substance also corrects the hemoconcentration, hypoglycemia, and decreased sodium chloride levels of these animals.

That resistance to the hypoglycemic and convulsive effects of insulin could be conferred by the administration of anterior pituitary extracts has been known since the original work of Houssay & Potick in 1929. Young has termed this a "glycotropic" action and has indicated that a separate anterior pituitary factor is the responsible agent. Jensen & Grattan (55) have shown that resistance to insulin shock could be conferred on mice (a) by crude anterior pituitary extract, (b) by the adrenotropic hormone, (c) by cortical extract, and (d) by corticosterone but not by desoxycorticosterone. They suggest that the "glycotropic" factor of Young is identical with the adrenotropic hormone and the effective hormone is some member (or members) of the adrenal cortical steroids. In a further paper Grattan & Jensen (1) have correlated the anti-insulin action of these substances with their ability to increase the liver glycogen of fasting mice and have clearly shown the identity of the two effects since only those cortical steroids that increased liver glycogen had an anti-insulin action. Finally, Grattan, Jensen & Ingle (56) have shown that while the adrenotropic hormone is inactive in protecting adrenalectomized mice against insulin or in promoting liver glycogen deposition, the active cortical steroids still retain their potency in these animals.

While their conclusion that the anti-insulin action of the anterior pituitary is mediated by the adrenal cortex and that the effective agent is a cortical hormone would seem to be justified by the evidence, nevertheless it might be pointed out that the essential factor in alleviating insulin convulsions is the level of the blood glucose. The blood glucose level can be maintained either (a) by increasing the rate of glucose formation, the effect they observed, or (b) by any agent that inhibits glucose utilization. Consequently, there may be two types of "glycotropic" action, the first of which these authors have studied. The other may be the consequence of a pituitary factor that acts directly on the tissues and by inhibit-



ing glucose utilization maintains the blood glucose at levels sufficiently high to prevent insulin convulsions. As in many other problems of the anterior pituitary a clear distinction between the tropic and direct effects of this gland has yet to be shown.

Before discussing the various suggestions that have recently appeared concerning the nature of the effect of cortical hormones on carbohydrate metabolism, it is of value to review another type of experimental evidence that not only bears on this point but also again indicates a striking difference between the various substances and fractions derived from the adrenal cortex.

In a series of papers Ingle has shown that the muscles of adrenalectomized rats cease to respond far sooner to direct stimulation than do those of normal animals and that this effect may be used as a method of determining the efficiency of cortical hormones. Winter & Knowlton (57) have confirmed this finding and have also shown by recording isometric contractions that the rapid decline in the tension produced by the muscles of adrenalectomized animals is due to a deficiency existing in the muscles themselves: it is not merely a reflection of the declining state of the organism when subjected to stress.

Ingle & Kendall (58) have found that the amorphous fraction of cortical extracts, while effective in maintaining the life of adrenalectomized animals was much less active in maintaining muscle work, particularly in comparison with 11-dehydro-17-hydroxycorticosterone. Ingle (59) has further emphasized the difference between even the crystalline compounds in maintaining the working capacity of skeletal muscle. 11-Desoxycorticosterone, while the most active in life maintenance, had only a feeble effect on muscle work in comparison to 11-dehydro-17-hydroxycorticosterone, a compound whose ability to maintain life is inferior to that of 11-desoxycorticosterone. In another paper Ingle (60) has shown that the ineffectiveness of desoxycorticosterone acetate is not due to its insolubility, as the water-soluble phosphate salt is no more effective. Nor is the lack of activity due to the absence of an hydroxyl group at carbon 17 since 11-desoxy-17-hydroxycorticosterone is also relatively inactive. It seems quite clear that the presence of an oxygen atom at position 11 is essential not only for the ability of these compounds to increase the working capacity of muscles but also, from the evidence reviewed above, for their effect on carbohydrate and protein metabolism.

This view is further supported by the observation of Ingle &



Lukens (61) that the fatigue of muscles of adrenalectomized rats can also be relieved by the administration of glucose to about the same degree as produced by the active cortical steroids. The effect produced by glucose was not due either to the volume of fluid administered nor to its osmotic activity since isomolar concentrations of sucrose or sodium chloride were much less effective. Nevertheless, the injection of sucrose and sodium chloride did bring about some improvement, an effect which is attributed to the volume of fluid introduced. The injection of epinephrine also improved the rate of work significantly and this combined with glucose infusion restored the capacity of the muscles to almost normal levels. Evidently there is a close connection between the ability of the muscles to continue long sustained work and the capacity of the organism to furnish sufficient supplies of glucose either from preformed or noncarbohydrate sources.

In the papers quoted above Ingle has emphasized other differences in the activity of these steroids which seem to be related to their structure. Apart from the fact that 11-desoxycorticosterone is much more active in maintaining the life of adrenalectomized rats it was also found that its administration led to an increased body weight while the injection of 11-dehydro-17-hydroxycorticosterone was followed by weight loss. Wells & Kendall (62) have reported a similar retardation of the growth rate of young rats when this compound was administered in daily doses of 1 mg. Such treatment also brought about an atrophy of the adrenals and thymus. It is probable that the retardation of growth is associated with the "diabetogenic" properties of this hormone.

Finally, mention should be made of the studies of Anderson *et al.* (63, 64) on the metabolism of adrenalectomized rats maintained by the use of sodium chloride alone. They report that, provided the quantities of sodium chloride given were not excessive, the animals were able to form liver glycogen from glucose as well as normal animals. This is at variance with the observations of Britton & Corey (65) on adrenalectomized cats treated with sodium chloride but is in harmony with the results of other investigators. In another series of experiments they report that the nitrogen excretion of fasting adrenalectomized rats given tap water to drink was very much less than that of normal animals. However, if ample amounts of sodium chloride were given the difference was much less although from their published figures



(their Table I) a discrepancy still existed even if the animals were given desoxycorticosterone during the fasting period. In other experiments where the animals were primed with the hormone prior to the fast the nitrogen excretion was normal for the first three or four days and then fell below normal.

#### THE MECHANISM OF ACTION OF THE ADRENAL CORTICAL HORMONES ON CARBOHYDRATE AND PROTEIN METABOLISM

Kendall (66) has discussed the function of the adrenal cortex and has outlined the large number of physiological processes over which this endocrine gland has been reported to exert an influence. These may be classified into three main groups: (*a*) control of electrolyte and water metabolism including the regulation of renal function, (*b*) control of carbohydrate and protein metabolism including the influence of the gland on the working capacity of muscles, (*c*) resistance to stresses of various kinds including bacterial toxins, histamine, shock, water intoxication, exposure to low temperatures, and low oxygen pressures.

It is not apparent that the crystalline steroids derived from the adrenal cortex differ in their relative effects on electrolyte and carbohydrate metabolism. Thus, the electrolyte and water metabolism are influenced more by desoxycorticosterone than by compounds of the corticosterone type, while carbohydrate metabolism as well as the working capacity of skeletal muscles is but slightly influenced by the former but very markedly by the latter steroids. The third group outlined above (group *c*) contains a large number of conditions that probably demand different physiological adjustments on the part of the organism. For some of these desoxycorticosterone is the most effective, while for others, the corticosterone group is required. A further discussion of some of these conditions will be found below. Finally, the solution remaining after all crystalline material has been removed from cortical extracts still has marked biological activity. This is the "amorphous fraction" of Kendall and is stated to be particularly effective in the regulation of renal function and the maintenance of life of adrenalectomized animals. The statement that the renal function of these animals is maintained by this fraction would seem to imply that it can also regulate the electrolyte balance. This fraction does not have any effect on carbohydrate metabolism.

Kendall's paper should be consulted in full since it contains



a great deal of information on the relative activities of these various adrenal steroids and fractions.

Hartman & Spoor (52) also find that cortical extracts can be fractionated into two parts, one of which, the "sodium factor," has a marked effect on the electrolyte balance while the other, termed "cortin," is necessary for life maintenance and is the most active in its effects on carbohydrate metabolism.

It is now known that not only the adrenal steroids but also certain estrogenic hormones, including the synthetic hormone stilbestrol, are able to cause a retention of sodium chloride and an increased potassium excretion in normal animals. Consequently, although desoxycorticosterone is the most effective in this regard, this particular property can hardly be termed specific for the adrenal cortical hormones since it is shared by such a large number of steroids from other sources. Neither can the ability to maintain the life of adrenalectomized animals be regarded as specific to the adrenal steroids since both desoxycorticosterone and progesterone are equally effective along with 11-dehydrocorticosterone in maintaining adrenalectomized rats (67) while 17-hydroxycorticosterone is much less effective. The estrogenic hormones, although influencing sodium balance in normal animals, are exceedingly toxic to those lacking their adrenals and actually shorten their life (68). Even the implantation of anterior pituitary tissue into adrenalectomized rats will prolong their life presumably by the increased secretion of progesterone that it produces (69).

At the present time the effects of the corticosterone type of compounds on carbohydrate and protein metabolism and the working capacity of muscle appear to be specific inasmuch as desoxycorticosterone, progesterone, and the estrogens do not produce similar effects when given in comparable amounts. Even to this statement, however, there are exceptions. Ingle (26) has reported that stilbestrol is diabetogenic in both normal and partially depancreatized rats, and Gaunt and his collaborators (27) find that estrogens augment the glycosuria of partially depancreatized ferrets. Although progesterone was inactive in diabetic animals, they had previously reported (70) that large doses of this hormone would increase the liver glycogen of normal ferrets. Griffiths, Marks & Young (25) also state that both the natural estrogens and diethyl stilbestrol will increase the liver glycogen of fasting rats. It should be remembered, however, that this effect of estrogens may be due to their secondary action on the adrenal cortex.



Nevertheless, in spite of their apparently specific effects on certain phases of carbohydrate and protein metabolism even corticosterone and its allied compounds will also influence the excretion of sodium and potassium so that at the present time not one compound isolated from the adrenal cortex can be said to be entirely specific in its effects. None of them is as effective in controlling the many phases of the disordered metabolism of the adrenalectomized as an extract containing a mixture of both the crystalline and amorphous principles of the gland. This situation has led Kendall to suggest that the adrenal cortex can vary the type of hormone that it secretes to the immediate needs of the organism.

The striking effects of adrenalectomy and the injection of corticosterone and allied compounds on the carbohydrate and protein metabolism of normal animals have led several investigators to study the metabolism of tissue slices taken from adrenalectomized animals.

Crismon & Field (71) found that when allowance was made for the hydration of the tissues of adrenalectomized animals that the oxygen consumption of the brain and muscle were essentially normal but that of the kidney was decreased about 18 per cent on a dry weight basis. This decrease was observed in kidney slices taken from the fourth to the eighth day after operation. Tipton (72) not only confirmed the decreased respiration of kidney slices but also observed that the respiration of liver slices was decreased to an equal degree. In addition it was found that the liver slices had a decreased ability to oxidize both pyruvate and succinate. Liver slices from normal rats whose food intake was limited to the amount ingested by the operated animals had a slightly decreased respiration but a normal ability to utilize pyruvate and succinate. Simultaneously with the publication of Tipton's paper there appeared that of Russell & Wilhelmi (73) who investigated not only the oxygen uptake of kidney slices from adrenalectomized animals both with and without such substrates as pyruvic, succinic, and  $\alpha$ -keto glutaric acid but also the comparative ability of the tissue to deaminate the corresponding amino acids, alanine, and glutamic acid. They found that the rate of oxygen uptake with any of these substrates was significantly less than normal. Furthermore, the rate of deamination of the amino acids as judged by ammonia production was also less than normal. These defects could be restored to normal if the animals were previously treated with cortical extract. Indeed, if intensive treatment was instituted rates



greater than normal were observed and there were indications that such treatment when given to normal rats also increased the rate of oxygen uptake and deamination in the presence of the amino acids. These observations are important inasmuch as there is a considerable body of evidence to indicate that the cortical hormones are concerned with some phase of gluconeogenesis from protein.

In a second paper Russell & Wilhelmi (74) have extended their previous observations and now report that while the rate of glucose utilization and the rate of carbohydrate formation from succinic and pyruvic acid in kidney slices are unaffected by adrenalectomy there is a significantly lower rate of carbohydrate formation from alanine and glutamic acid. This indicates that an important factor limiting the rate of gluconeogenesis after adrenalectomy is the rate of deamination of amino acids. This conclusion is in part contrary to that reached by Thorn and his colleagues (75) who injected lactic acid, pyruvic acid, or alanine into phlorhizinized rats and by use of the G/N ratio of fasting uninjected controls together with the observed glucose and nitrogen excretion calculated that after adrenalectomy only 26 per cent of glucose was formed from lactic acid as compared to 74 per cent in normal animals. The figures for pyruvic acid were 34 per cent and 102 per cent and for alanine 57 and 90 per cent. They regard the defect in gluconeogenesis to be an inability of the organism to convert the 3-carbon derivatives into glucose. However, one might well question the emphasis that should be placed on differences of this kind, particularly under the experimental conditions employed. Untreated adrenalectomized animals frequently react very unfavorably to the intraperitoneal injection of such quantities of fluid as were employed in these experiments. In a further preliminary communication Thorn and his associates (76) report that liver slices from adrenalectomized rats form carbohydrate from glucose, lactate, and pyruvate at a normal rate. This is in agreement with the finding of Russell & Wilhelmi for the kidney. In their experiments, however, alanine failed to form significant amounts of glucose in slices from either normal or adrenalectomized animals so that the relative rates of deamination and carbohydrate formation from this amino acid could not be determined.

Excluding the experiments on phlorhizinized animals there is evidently fairly substantial agreement among these investigators



that the residue from the deamination of amino acids can be converted into glucose at a normal rate both by the kidney and liver tissue of adrenalectomized animals. The results of Russell & Wilhelmi suggest, in accord with the experience encountered in the whole animal, that adrenalectomy retards the rate of deamination of amino acids and in consequence the rate of glucose formation from protein. Whether this is the only change in the normal metabolic processes that is brought about by adrenalectomy is uncertain and indeed other experiments have suggested that the cortical hormones regulate other phases of metabolism.

Seckel (77) has reported that cortical extract inhibits glycogenolysis in surviving rat liver slices and concludes that one function of the adrenal cortex is to inhibit the glycogenolytic enzymes. This suggestion is an extension of the views of Britton and his colleagues who have long maintained that an inability to maintain adequate liver glycogen stores (and other carbohydrate levels) is a characteristic consequence of the loss of cortical hormone. Recently Britton & Corey (65) reported that insulin fails to induce glycogen storage in the liver and muscles of adrenalectomized cats given glucose. It is difficult to reconcile these observations with those of others who have found that salt-treated adrenalectomized rats and dogs will survive for long periods with approximately normal carbohydrate levels and when given glucose they will dispose of it in part by storage as glycogen (78). In further support of their views Corey & Britton (79) report that if cortical extract is perfused along with glucose through isolated rat liver glycogenolysis is retarded. In the perfused cat liver, when the cortical extract was added to a Ringer gum-glucose perfusate, an actual increase in the glycogen content was observed. Indeed, the authors state that a 100 per cent increase might occur in ten or fifteen minutes. Desoxycorticosterone was inactive and the addition of insulin did not cause an increase in liver glycogen. On the contrary, the usual result was a decrease.

At the present time, therefore, there is evidence that the cortical hormones that influence carbohydrate metabolism may do so (a) by inhibiting the peripheral utilization of glucose, (b) by inhibiting liver glycogenolysis or accelerating the conversion of glucose to glycogen, (c) by controlling the rate of deamination of amino acids and in consequence the rate of gluconeogenesis from protein. Which of these effects, if any, is responsible for the maintenance



of the working capacity of muscle and the ability of the kidney to perform sufficient osmotic work to maintain a normal electrolyte balance is not known but it is entirely possible that there is an intimate connection between them.

#### THE RELATION OF THE CORTICAL HORMONES TO CONDITIONS OF STRESS

Under this heading may be grouped a number of conditions in which it has been claimed that the adrenal cortex is called upon to aid the organism in making the necessary physiological adjustments. Most of the experiments that have been carried out to support such claims have been done on adrenalectomized animals and in these there is no doubt that proper treatment with cortical hormones enables them to survive circumstances under which untreated animals speedily succumb. The other and equally important problem as to whether supernormal resistance to adverse circumstances can be conferred on normal animals by the administration of cortical hormones is still an unsettled one, although there are indications in some instances that beneficial results might be expected.

*Histamine.*—It is now well known that the resistance of the rat and other animals to injected histamine is much decreased by adrenalectomy and that treatment with cortical extract will restore this to normal. Karady, Rose & Browne (80) now report that the histaminase content of the rat lung is decreased by adrenalectomy but may be restored by the injection of cortical extract. As the authors comment, however, the decrease in this enzyme would appear to be entirely inadequate to explain the observed sensitivity of these animals to histamine. In another paper Rose & Browne (81) find that while the histamine content of the liver and lung are only moderately increased after adrenalectomy the content of the gastrointestinal tract is increased to a degree that might account for the frequent occurrence of ulceration in these organs after adrenalectomy. Wilson (82) has also observed an increase in the blood histamine of adrenalectomized rabbits; it decreased, however, within one hour after the injection of cortical extract. Noble & Collip (83) have studied the toxicity of histamine in normal, adrenalectomized and hypophysectomized rats. As others have reported they found that the intact rat survives the injection of relatively large doses while in adrenalectomized or hypophysectomized



animals an injection equivalent to 650 mg. per kilo of body weight killed 85 per cent of the animals in from six to twenty-four hours. The injection of desoxycorticosterone afforded no protection to hypophysectomized rats but almost complete protection could be obtained by previous treatment of the animals with a corticotropic fraction from the anterior pituitary. On the other hand the treatment of adrenalectomized rats with desoxycorticosterone lowered the mortality rate. No experiments with corticosterone or allied compounds are reported.

*Shock.*—It has been well established that adrenalectomized dogs are particularly susceptible to such shocking procedures as trauma to muscles, intestinal manipulation, intraperitoneal injection of glucose or large quantities of epinephrine. Selye (84) reports that corticosterone but not desoxycorticosterone is very effective in combating shock produced in normal rats by clamping of the viscera, or formaldehyde injection. The amounts of corticosterone given was 2 mg. in divided doses. Swingle and his colleagues (85) have recently reported their observations on the comparative prophylactic value of these steroids in the circulatory failure induced in adrenalectomized dogs by hemorrhage and trauma. They find desoxycorticosterone to be effective in preventing shock following hemorrhage, but not effective in the trauma associated with bilateral adrenalectomy in one stage. Corticosterone or cortical extract will, however, protect animals subjected to intestinal trauma. An exceedingly interesting observation is that local blocking of the nerve elements in the vicinity of the adrenals by procaine prior to operation prevents shock.

So far Selye's experiments are the only ones in which it is claimed that normal animals can be protected against the deleterious effects of trauma by a cortical hormone, although Rhoads, Wolff & Lee (86) believe that cortical extract in frequent doses of 5 to 10 cc. is of value in the treatment of patients with severe burns. However, such treatment is only of value if given along with infusions of plasma.

*Water intoxication.*—Closely allied to the susceptibility of adrenalectomized dogs to hemorrhage is their comparative inability to dispose of large quantities of water given by stomach tube. Swingle *et al.* (87) have shown that this reduced tolerance can be corrected by priming doses of desoxycorticosterone acetate. Eversole & Gaunt (88) have confirmed this effect in the rat but point



out that desoxycorticosterone is only one fifth as effective in protecting against water intoxication as a concentrated cortical extract. Corey & Britton (89) report that the chronic mild diabetes insipidus of hypophysectomized rats is greatly increased by the injection of desoxycorticosterone. This effect they state is antagonized by posterior pituitary extract. It will be recalled that Loeb and his collaborators (90) found that the prolonged administration of desoxycorticosterone to normal dogs resulted in polydipsia and polyuria. This was also found by Corey & Britton to occur in normal and adrenalectomized rats. These authors maintain, on the basis of this and previous publications, that a normal salt and water metabolism is in part determined by the antagonistic but balanced relationship between adrenal and pituitary factors. That other hormonal factors may be involved is indicated by Schweizer *et al.* (91) who found that the diabetes insipidus of hypophysectomized rats could be corrected by injections of anterior pituitary extract and that this effect was not mediated by the adrenal cortex. Selye & Bassett (92) who had previously shown that progesterone had a diuretic action in hypophysectomized rats also report the diuretic action of desoxycorticosterone both in normal and hypophysectomized rats. They also state that this is not due to the kidney hypertrophy produced by these steroids since testosterone which is the most active in this regard does not cause a diuresis.

*Typhoid vaccine.*—Adrenalectomized rats are quickly killed by doses of typhoid vaccine that do not harm normal animals yet they may be protected by adequate treatment with cortical extract. Ettelson (93) has now shown that desoxycorticosterone is not capable of conferring such protection but it may be presumed that corticosterone and its allied compounds would be effective.

#### THE ADRENAL CORTEX AND INTESTINAL ABSORPTION

Verzar's theory that the adrenal cortical hormones are concerned with phosphorylation processes in the intestine involving not only fats and carbohydrates but also vitamin B<sub>2</sub> has been studied in several papers.

Houssay, Foglia & Fustinoni (94) found in the toad that the selective absorption of glucose, fructose, and galactose was not modified by adrenalectomy nor by destruction of the principal (anterior) lobe of the hypophysis. Even when other marked signs of adrenal insufficiency were present the absorption of these sugars



was normal. Marrazzi (95) studied the comparative absorption of glucose and xylose in the adrenalectomized rat. She found the absorption of glucose to be decreased but not to the same degree as reported by Verzar's group. However, the sham-operated animals and normal animals in which the food intake was limited to that of the operated group also showed similar reductions in the rate of glucose absorption. She concludes that this decreased absorption might be as well attributed to the effects of anorexia as to any specific loss of cortical hormone. In contrast to the results of Althausen *et al.* (96) she found that the liberal administration of sodium chloride did not prevent a decrease in the rate of glucose absorption in operated animals.

Barnes, Miller & Burr (97) making use of the high spectral absorption quotients of conjugated fatty acids have followed not only the rate of absorption but also the rate of incorporation of tagged fatty acids into the neutral fat and phospholipids of the intestinal mucosa in both normal and adrenalectomized rats. If anything, the rate of fat absorption was greater in the operated animals while the rate of incorporation of fatty acids into neutral fat or phospholipids was the same. In a second paper (98) the rate of fat transported to the liver was studied by the same methods. They found that while the incorporation of the tagged fatty acids into the liver phospholipids was not altered by adrenalectomy their deposition into the neutral fat fraction was greatly impaired. This evidence, of course, lends no support to Verzar's view that adrenalectomy impairs phosphorylation processes involving fatty acids but does indicate some disturbance in other phases of fat metabolism, since it was found that treatment with cortical extract returned to normal the rate of fatty acid incorporation into the neutral fat fraction of the liver. Bavetta *et al.* (99) fed hydrogenated cotton seed oil to adrenalectomized rats and found a definite decrease in the rate of absorption that was corrected by the injection of cortical extract.

One of the most interesting suggestions arising from Verzar's theory of cortical function was that in the absence of the hormone the animal was unable to phosphorylate riboflavin and, consequently, would be deprived of vitamin B<sub>2</sub>. Bruce & Wein (100) have studied the effects of combined riboflavin and cortical deficiency in the rat and failed to obtain evidence to support Verzar's view. When the rats lacked both riboflavin and cortical extract



the administration of riboflavin alone increased their survival somewhat but the injection of small amounts of cortical hormone also increased the survival although the riboflavin deficiency was still present. The administration of riboflavin phosphate (vitamin B<sub>2</sub>) which, according to Verzar, should prolong indefinitely the lives of adrenalectomized animals, gave no better results than riboflavin itself.

One of Verzar's colleagues, Laszt, has suggested that the phosphorylation of thiamin to form cocarboxylase is also dependent on the presence of cortical hormone. Ferrebee (101) has tested this hypothesis in the rat, together with a similar study of vitamin B<sub>2</sub>. After adrenalectomy the animals were given a 10 per cent glucose solution containing 10  $\mu$ g. of thiamin and 5  $\mu$ g. of riboflavin. The survival periods of some animals were increased by adding sodium salts to this solution, while other animals were maintained by the use of low potassium diets. After various intervals, which should have been long enough to deplete the vitamin stores if the theory was correct, the treatment was withdrawn and when the animals lapsed into adrenal insufficiency the livers and kidney were removed and their content of vitamins B<sub>1</sub> and B<sub>2</sub> determined. No difference was found as the result of adrenalectomy.

Clark (102) has also shown that massive doses of thiamin hydrochloride or its pyrophosphate (cocarboxylase) exert no beneficial action in adrenalectomized guinea pigs. Riboflavin was also without effect. In addition, this author, as though anticipating similar claims for other members of the vitamin family, showed that sodium nicotinate, pyridoxin, factor W, pantothenic acid, and filtrate factor were also ineffective in alleviating the usual course of events in adrenalectomized guinea pigs.

The evidence reviewed here together with the work published earlier would seem to leave no doubt that the control of phosphorylation processes is not a function of the adrenal cortical hormone. It may be suggested from the work of Bruce & Wien (100) that the favorable results found by Verzar to follow the administration of vitamins B<sub>1</sub> and B<sub>2</sub> to adrenalectomized rats were due to the animals receiving a diet that was deficient in these factors.

#### THE RENOTROPIC ACTION OF CERTAIN STEROIDS AND THEIR EFFECT ON EXPERIMENTAL UREMIA

In 1939 Selye (103) reported that the injection of testosterone into mice was followed by a marked increase in the weight of the



kidney, mainly due to hypertrophy of the cells of the proximal and distal tubules. The rat kidney was not nearly as sensitive to the effect of this hormone as that of the mouse. These studies on the mouse were later confirmed by Pfeiffer, Emmel & Gardner (104) who showed in addition that certain estrogens also produced a slight increase in kidney weight. They concluded that testosterone brought about a general hypertrophy of the kidney rather than a regional one.

Selye (105) has also reported that desoxycorticosterone acetate has a similar "renotropic" action in rats and mice and this has been confirmed in the rat by Ludden, Kruger & Wright (106). The latter also observed an increased kidney weight after the injection of testosterone propionate and estradiol benzoate. Their evidence indicated that desoxycorticosterone acetate and testosterone propionate brought about an absolute increase in the renal substance as judged by the increased dry weight while the estrogen increase was largely due to hydration of the tissue.

The doses required to produce optimal effects in the rat were 1.0 to 10.0 mg. a day of testosterone propionate for twenty-one days, or 1.0 mg. a day of desoxycorticosterone acetate for forty-two days.

Selye (107) has recently reviewed what is known concerning the effects of various endocrine glands upon the size and structure of the kidney and has added further observations of his own. He reports that not only desoxycorticosterone and testosterone but also progesterone exert a renotropic action. In addition, removal of the hypophysis does not prevent this effect. Nevertheless, the kidney undergoes marked involution after hypophysectomy and this cannot be entirely prevented by administration of these steroids. The injection of follicle stimulating or luteinizing extracts of the anterior pituitary also exert a "renotropic" action in the hypophysectomized rat although again they are unable to restore the kidney to its normal size even if they are combined with the injection of testosterone. Selye states that in his opinion it is unnecessary to postulate a specific pituitary "renotropic" factor since other hormones, such as the growth promoting agent and the thyroid hormone, are also known to control the size of the kidney.

These morphological studies have gained added interest by the reports of Selye and his colleagues (108, 109, 110, 111) that the previous injection of either testosterone or desoxycorticosterone prolonged the survival of rats and mice after (a) poisoning with mercuric chloride, (b) ligation of a ureter, or (c) total nephrectomy.



In the first series of experiments (108), ten female mice received 0.1 cc. of a 0.25 per cent solution of mercuric chloride daily. All but three were dead on the fifth day and the kidneys of all showed the typical effects of mercury poisoning. Another ten mice received daily for six days prior to the injection of mercuric chloride, 0.1 cc. of free testosterone in oil. Except for one animal that died of pneumonia all were alive and in apparent good health on the fifth day when they were killed for histological examination. Their kidneys not only showed hypertrophy but also a remarkable absence of the tubular degeneration present in the untreated group. In another experiment one group of mice were given 3 mg. of testosterone daily. Of these, eight were alive sixty-five days after discontinuing the mercuric chloride injections while all the untreated animals were dead by the eighth day.

In the experiments in which one ureter was ligated the injection of testosterone delayed the atrophy of the kidney parenchyma that normally follows this procedure (110).

The previous injection of desoxycorticosterone in doses of 5 mg. daily is stated by Selye (109) to prolong the life of rats subjected to bilateral nephrectomy. While all the control animals were dead sixty-two hours after operation only four of ten injected animals had died. In mice even better survival was observed. All the controls died within twenty-four to thirty-one hours while only one of the treated animals had succumbed. In these experiments some extrarenal effect of the steroid is, of course, responsible but the nature of this is not discussed. In a further paper Dosne (111) has confirmed the original findings and reported that the optimal amounts of desoxycorticosterone were 2 mg. a day for three days in mice and 5 mg. a day for three days in rats. These are considerable quantities of hormone for animals of this size. So far only preliminary studies have been published of the alterations in the blood chemistry in the treated and untreated animals (112). The average nonprotein nitrogen in a group of untreated rats was 204 mg. per cent and 170 mg. per cent in those treated with corticosterone. This difference was statistically significant.

Until further work has been done it is impossible to draw any definite conclusion as to the peculiar effect of desoxycorticosterone that is indicated by these studies. However, it is well known that this substance has a marked effect on electrolyte metabolism and if given in large amounts depletes the organism of potassium. In-



deed, Ragan *et al.* (90) have found that large doses given to normal animals (dogs) produce a syndrome similar to that seen in diabetes insipidus but with an elevated serum sodium and reduced serum potassium. If the potassium intake in the diet is reduced the animals develop muscular weakness which is probably associated with the potassium depletion.

Now in the experiments of Selye *et al.*, the desoxycorticosterone was always given in considerable amounts for some days prior to the nephrectomy; consequently they began with reduced potassium stores which may account for their prolonged survival. This conclusion seems to be warranted by the observation of Hoff, Smith & Winkler (113) that the factor precipitating the death of animals after bilateral nephrectomy is the potassium accumulation in the serum. Furthermore, Durlacher, Darrow & Winternitz (114) have observed that the administration of a low potassium diet to rats prior to total nephrectomy also increased the survival period. The levels of serum potassium and nonprotein nitrogen were not elevated to the same degree as in animals that had previously ingested an average diet, [cf. Selye & Nielsen (112) quoted above]. Experiments that also bear on this point are to be found in the paper by Hartman & Dubach (115). They observed that the survival of rats subjected to combined adrenalectomy and nephrectomy was much less than those in which the kidneys alone were removed. The administration of cortical extract after the combined operation raised the survival to that of nephrectomized animals but there was no indication that it increased beyond this period.

#### MISCELLANEOUS

Wells & Kendall (116) have found that the administration of corticosterone is followed by atrophy of the adrenal cortex and thymus of the normal rat. Desoxycorticosterone did not do this nor did the amorphous fraction from the extract which had been freed from all crystalline steroids. In the same paper they report that the daily injection of desoxycorticosterone acetate into rats was followed by a large decrease in the level of serum potassium. Corticosterone did not alter the potassium level although both compounds increased the level of serum sodium. Clausen (117) has found that the administration of large amounts (4 mg. a day) of progesterone to rats also brings about atrophy of their adrenal and thymus glands. This result is surprising in view of the failure of Wells & Kendall



to observe atrophy after the daily administration of 3 to 10 mg. of desoxycorticosterone acetate.

Selye (118) has described an interesting effect of the intraperitoneal injection of large amounts (5 to 35 mg.) of desoxycorticosterone or progesterone into normal rats and mice. Within fifteen minutes the females but not the males were deeply anesthetized. The mortality, however, with the larger doses was high. Testosterone also exhibited this anesthetic action but its effect was more delayed.

Cantarow & Rakoff (119) find that the injection of desoxycorticosterone acetate or progesterone increases the rate of entrance of sodium chloride into the peritoneal cavity of dogs that have received isotonic glucose solution. They suggest that these observations support the view that the electrolyte metabolism of the adrenalectomized animal is disturbed by reason of an alteration in membrane behavior and that this is not limited to the kidney alone. However, in another communication (120) they state that this increased rate of transfer of sodium chloride is also brought about by estradiol, diethylstilbestrol and testosterone propionate. Furthermore the effect could not be shown in rabbits.

Stein & Wertheimer (121) find that the absorption of sodium chloride from the small intestine of adrenalectomized rats maintained on sodium chloride is much less than in normal animals and does not occur against the concentration gradient. The injection of desoxycorticosterone returned the animals to normal. These experiments, together with those on the influence of these substances on the renal excretion of sodium chloride, indicate that a number of steroids, apart from those of the adrenal cortex, are able to influence electrolyte metabolism. It may be suggested that the ability of some of them to maintain the life of adrenalectomized animals is related to their effect on the electrolyte balance. Grollman *et al.* (122) find that while desoxycorticosterone acetate and certain estrogens elevate the blood pressure of rats this does not follow the injection of cortical extract. This has been confirmed by Swingle *et al.* (123). Grollman *et al.* suggest that the hypertensive action of these steroids is due to the renal damage that they cause.

Zwemer *et al.* (124) claim that certain cardiac glycosides (strophanthin) have effects that resemble those of the cortical hormones. They claim that they lower serum potassium and raise the blood glucose and also will protect animals against potassium



poisoning and insulin shock. They had previously stated (125) that this glycoside would prolong the lives of adrenalectomized animals, a claim that as far as mice are concerned is disputed by Dorfman (126).

Mills *et al.* (127) report that the necrosis of the adrenals that occurs in rats on certain types of purified diets is prevented by the addition to the diet of pantothenic acid, a conclusion that was reported a little earlier by Daft *et al.* (128).

Spoor, Hartman & Brownell (129) state that the adrenal cortex contains a lactation factor which they term cortilactin. This is prepared by isoelectric precipitation and brings about stimulation of the crop sac of pigeons in a manner similar to that of prolactin. It also supports lactation in adrenalectomized rats. It has no effect on the liver glycogen and apparently does not maintain the life of adrenalectomized animals.

## THE PANCREAS

### THE MODE OF ACTION OF INSULIN

Gemmill has published an interesting series of papers demonstrating that insulin increases the quantity of glycogen deposition in isolated rat diaphragm suspended in a Ringer glucose medium (130, 131, 132, 133). The increased deposition of glycogen is not associated with an increased oxygen consumption nor with an increased respiratory quotient. The amount of glycogen deposition increases with increasing glucose concentration in the medium and is further enhanced when insulin is present. If glucose is replaced by other sugars or such substances as succinate, lactate, or citrate no glycogen is deposited nor does the addition of small quantities of proteins induce any synthesis. Hechter, Levine & Soskin (134) have confirmed these observations and in addition point out that the insulin enables the tissue to form glycogen at low glucose concentrations for if the hormone is not present a three or four fold increase in glucose concentration in the medium is necessary for the formation of comparable amounts of muscle glycogen. However, in their experiments the addition of insulin to a medium containing 400 mg. per cent of glucose had practically no effect on the glycogen formation. In Gemmill's experiments, however, the addition of insulin when the glucose content of the medium was 500 mg. per cent still produced a notable increment in glycogen deposi-



tion. Consequently, although Hechter *et al.* on the basis of their experiments regard insulin as influencing only the rate at which glucose enters the cell from without, the work of Gemmill suggests, at least under his experimental conditions, that the hormone is actively concerned with glycogen formation from glucose.

Stare & Ricketts (135) have studied the effect of insulin on the respiration of minced human muscle taken from diabetic subjects of various types. The oxygen uptake of muscle from most patients did not differ from that of normal human muscle, but in the case of one "insulin sensitive" diabetic the addition of insulin caused a 40 per cent increase.

Although the studies were carried out on intact normal and depancreatized rats, Drury (136) has suggested that an important action of insulin is to promote storage of glucose and that it may also promote the transformation of carbohydrate into fat, a conclusion that is based, in part, on the observation with Greely (137) that the glucose utilization of depancreatized-hepatectomized rabbits is the same as that of normal animals after evisceration.

#### MISCELLANEOUS

Young (138) and Lawrence & Madders (139) have investigated the alleged beneficial influence of certain estrogenic substances on experimental diabetes and human diabetes. Young finds them to be without effect on the glycosuria of dogs rendered diabetic with anterior pituitary extract or pancreatectomy, while Lawrence could not observe any beneficial effect of stilbestrol in five diabetic women of menopausal age. Since estrogens have also been reported to aggravate experimental diabetes and, in the case of stilbestrol, to induce glycosuria in normal animals (cf. above) it is difficult to reconcile these very conflicting reports.

Gellhorn *et al.* (140) describe a sensitive method for the assay of insulin based on the use of adrenomedullated and hypophysectomized rats. With these animals quantities of insulin of the order of 0.001 units per 100 gm. of body weight may cause convulsions and coma. By the use of this method they state that the normal content of insulin in human blood is 0.002 units per cc.

Griffiths (141) suggests that the well known antagonism between subcutaneously administered insulin and posterior pituitary extract is due to the decreased rate of absorption of insulin by reason of the vasoconstriction that follows the injection of the



pituitary extract. If the insulin is given intravenously the pituitary extract in many instances fails to counteract the hypoglycemia.

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DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY  
YALE UNIVERSITY SCHOOL OF MEDICINE  
NEW HAVEN, CONNECTICUT



## THE PHYSIOLOGY OF REPRODUCTION

BY FREDERICK L. HISAW AND EDWIN B. ASTWOOD

*The Department of Biology and the Departments of Medicine and Pharmacology,  
Harvard University, Cambridge, Massachusetts*

The literature dealing with this branch of physiology has shown a marked annual increase both in number of publications and diversity and breadth of subject matter for the last twenty years. The vertebrates have received major attention, but more recently studies of the invertebrates (1) have become more numerous and of increasing importance. The past year has been exceptional as a result of the war, but even so it is not possible to include in the space of this review all the aspects of the subject contained in papers from this hemisphere. Consequently, certain topics have been selected for special emphasis while others are treated more briefly and references are made when possible to general papers rather than specific articles. About five hundred pertinent papers have knowingly been omitted because of the restricted space.

### THE ESTROUS CYCLE

The morphological aspects of the estrous cycle have been studied in great detail in a number of our common laboratory and domestic animals and the specific action on the female reproductive tract of a number of hormones known to be concerned has been quite well established. A point that is less well understood is the physiological interaction of the endocrines responsible for the development and coordination of the observed cyclic phenomena. The problem is also complicated by the fact that the secretion of certain of the interacting hormones is mediated at least in part by the nervous system and that the whole mechanism may be influenced or inhibited by nutritional and external environmental factors. The internal secretions that take direct part in regulating the estrous cycle are those of the ovary and the gonadotropic hormones of the pituitary while other endocrine glands, whose products are more directly concerned with the general metabolism of the body, exercise an indirect, though important, influence.

*Follicular activity.*—The reproductive activity of the ovary centers around the process of oögenesis and the development of Graafian follicles and corpora lutea. There is ample evidence that



oögenesis is a continuous process, beginning during prenatal life and continuing throughout the reproductive existence of the animal (2, 3, 4). There is much to be learned as to the controlling mechanism of oögenesis and follicular formation, but it is known that the process can proceed in the hypophysectomized rat up to the development of primary follicles. Also, the ovaries of immature rats do not develop follicles with diameters greater than  $200\mu$  until about the eighteenth day of life. When older rats are hypophysectomized, follicles larger than  $250\mu$  degenerate, while those up to this size are maintained in approximately normal condition (5). This indicates that an important physiological change takes place in the follicle at about the time an antrum is formed.

It is generally known that a fundamental difference exists between the primary follicles in the normal ovaries of young rats up to about thirteen days of age and those of older animals following hypophysectomy. The follicles of the young rats do not become greatly enlarged in response to pituitary gonadotropic preparations while those of the hypophysectomized animal do. From a morphological standpoint there is no apparent difference between the condition of these two types of follicles. The significance of this difference in follicular response is unknown but it suggests the possibility that follicular aging may be an important conditioning factor in the response of the follicle to pituitary stimulation. It is true that all the follicles in an ovary do not respond at the same time nor at the same dosage of pituitary gonadotropic hormone. There seems to be a difference in threshold of stimulation and a progressive availability of follicles. Lane & Davis (5) offer the suggestion that follicles smaller than  $200\mu$  in diameter might represent a reserve from which are drawn succeeding crops of follicles for maturation at successive estrous periods. If this be true, it seems of interest to add that this reserve can be replenished and maintained in the absence of the pituitary but development of follicles beyond 200 to  $300\mu$  is controlled by hypophyseal gonadotropic hormones.

The follicles coming to ovulation at any particular estrus in the rat and guinea pig take origin from primary follicles which may or may not contain small antra. During or shortly after the preceding estrus to the period of preovulatory swelling of the next succeeding estrus these follicles undergo a constant and progressive increase in volume (6). In the rat the rate of growth is constant regardless of whether the cycle is four, five, or six days in length. Consequently,



at the beginning of preovulatory swelling the follicles of a four-day cycle are smaller than those of a five or six-day cycle. It is interesting that the rate of follicular growth in the rat is approximately the same as that established earlier for the guinea pig. Thus the larger preovulatory follicles in the guinea pig are correlated with a longer cycle and a longer period of growth.

It seems that in all mammals ovulation is ushered in by a short period of very rapid follicular growth, commonly referred to as preovulatory swelling. The rate of increase in volume of the follicle at this time is about eight times that during the diestrus. The process starts in the rat at about the beginning of heat (sexual receptivity), which occurs in most animals about the time the first cornified cells appear in the vaginal smear, and continues until ovulation.

The time of ovulation is perhaps the most important reference point in the cycle from which such things as changes in the ovary, uterus, vagina, and sexual behavior may be dated and correlated. Ovulation occurs in the rat about ten hours after the beginning of heat which can be determined best by stimulating the display of the copulatory response (7). The vaginal condition varies with respect to ovulation but in most individuals ovulation occurs at about the time when cornification is complete.

*Luteal activity.*—The average length of heat in the rat is 13.7 hours (7) which is approximately five hours longer than that established for the guinea pig. Also, it should be noted that ovulation in the rat occurs before the end of heat. In most cases sexual receptivity begins with the first appearance of cornified cells in the vagina and ends after the period of cornification when nucleated cells are reappearing, but these conditions are less reliable criteria than the copulatory reflex for determining the length of heat.

The role of estrogen and progesterone in the induction of the copulatory reflex in guinea pigs has been well established and recently it has been found that these observations can be applied to the rat (8). From these results it seems logical to conclude that the appearance of heat marks the beginning of luteal activity and the secretion of progesterone. If this be true, it is notable that at this time luteal tissue as such has not yet appeared in the follicles. But certain early luteal changes have been detected in the follicular wall of preovulatory follicles of the rat (6), and also of the mouse (9), and cat (10).



This view receives support from studies of the influence of estrogen and progesterone on the accumulation of water in the tissues of the uterus (11). During the normal cycle the water content of the rat's uterus rises to a maximum shortly before proestrus, falls abruptly with the first appearance of cornified cells in the vaginal smear, and reaches a minimum at about the time of ovulation. The introduction of this period of dehydration coincides in general with the beginning of heat and preovulatory swelling. The conclusion that this decrease in water content is due to the secretion of progesterone by the follicles is based on the experimental fact that the injection of estrogen invariably results in a marked increase in tissue fluid with the exception of this period during which the estrogenic effect is strongly inhibited.

These observations throw considerable light on luteal function in the estrous cycle of the rat and quite probably have a broad application to the cycles of other animals. The most significant feature is the brief period during which progesterone is secreted, beginning with proestrus and ceasing at or soon after ovulation and before corpora lutea are fully developed. This indicates that luteal secretion and the formation of luteal tissue are two distinct processes that can proceed independently, and consequently a question is raised concerning the function of the luteinizing hormone of the pituitary (LH).

The part played by the luteinizing hormone (LH) in the development of corpora lutea and its cooperation with the follicle-stimulating hormone (FSH) in bringing about ovulation have been discussed at length in a number of recent papers (12, 13). The appearance of LH in effective amounts initiates preovulatory swelling of the follicle which is the first step in the process of luteinization during which ovulation usually but not invariably occurs. Also, the increase in the secretion of estrogen incident to preovulatory swelling is the result of a synergistic action of FSH and LH (12, 14), but there is convincing evidence that LH does not stimulate the secretion of progesterone (13, 15, 16).

It is generally conceded that the corpora lutea of hypophysectomized rats are nonfunctional and that LH cannot activate such corpora lutea to secrete progesterone. That sustained luteal function can be maintained in hypophysectomized rats by administering pituitary preparations that contain neither FSH nor LH has recently been established (13, 15, 16). Such treatment must be



started before or immediately following hypophysectomy as involution of the corpora lutea is so rapid that they become irreparably damaged within twenty-four hours after pituitary ablation.

The hormone responsible for luteal secretion has been called luteotrophin (13). It is easily separated from FSH, LH, and thyrotropin and fairly readily dissociated from the growth factor. It appears distinct from the adrenotropic hormone and the fact that the reaction is not influenced by adrenalectomy supports this view. Lactogenic preparations possess luteotrophic action (15, 16), but whether or not the lactogenic hormone is identical with luteotrophin is a question as yet unanswered.

The introduction of a third factor in the interrelationship of the ovary and pituitary necessitates a considerable change in the current concept regarding the controlling mechanism of the estrous cycle. This, as it relates to mammals, has been discussed elsewhere but a few remarks in this connection should be made concerning the lower vertebrates. The dependence of gonadal activity on the pituitary has been established in representative animals for all the vertebrate classes. In the smooth dogfish (*Mustelus canis*) ovulation requires at least several hours and perhaps days, and about sixteen to twenty ova are released from the ovary one at a time. Hypophysectomy prevents ovulation or interrupts it once it is started and pituitary implants will reinitiate it (17). A pituitary-gonadal relationship has been demonstrated in several species of teleost fishes (18, 19, 20, 21), while in amphibia experimental ovulation and the release of spermatozoa by pituitary implants and extracts has been developed into a common laboratory procedure. The most recent advancement is the discovery that ovulation and maturation of the ova can be induced in frog ovaries or ovarian fragments *in vitro* (22, 23). Atrophy and restorative changes in the gonads as results of hypophysectomy and pituitary implants have also been reported for reptiles (24) and birds (25).

These observations show clearly that gonadal activity in the lower vertebrates is under the control of the pituitary but they furnish little evidence as to the controlling mechanism. It is generally thought that the pituitaries of such animals secrete FSH and LH. This probably is true, but the evidence is not convincing as it is based almost entirely on reactions elicited by mammalian hormones. Also, the results of experiments in which the pituitaries of the lower vertebrates have been tested on mammals are quite



discouraging. The gonadotropic hormones of the pituitary are proteins and the difficulties encountered are probably the result of specific differences or foreign protein reactions.

However, corpora lutea are present in the ovaries of certain elasmobranchs and reptiles, while in amphibians they are absent and their existence in birds is doubtful. These luteal structures, when present, are not invariably associated with viviparity. They are found in the viviparous dogfish, *Mustelis canis* and *Squalus acanthias*, but are also present in the skate, *Raja erinacea*, which is oviparous (17). They have been reported in seven viviparous species of North American snakes belonging to the genera *Storeria*, *Potamophis*, *Thamnophis*, and *Natrix* (26) and in the South American species of the genera *Crotalus* and *Bothrops* (27). Corpora lutea have also been reported in two species of oviparous snakes, *Lampropeltis* and *Diadophis*, and also in the horned toad and snapping turtle (28).

These luteal bodies in the dogfish are apparently nonfunctional as their presence is not essential for the maintenance of pregnancy. Development of the embryos, absorption of yolk, and formation of a yolk sac placenta can proceed normally in the hypophysectomized smooth dogfish from ovulation until at least the fifth month of gestation (17). In snakes, however, indications of luteal function have been adduced. Ovariectomy during early gestation, removal of corpora lutea, and hypophysectomy resulted in resorption of embryos or abortion of dead young (26, 27, 29).

These observations should be repeated and extended as they are probably very important for the consideration of the evolution of viviparity. Judging from mammals, luteal function would denote the action of luteotrophin. If luteotrophin and prolactin are identical, one might expect to find luteal activity in birds (30), but so far no one has succeeded in demonstrating progesterone in any of the vertebrates other than mammals.

*Pituitary gonadotropic hormones.*—Recent reviews have analyzed the evidence for and against the concept that follicle stimulation and luteinization are the effects of two separate gonadotropic hormones (31, 32, 33).

Some workers feel that the various qualitative differences observable with different pituitary fractions can be explained on the basis of a single hypophyseal gonadotropic hormone (34, 35, 36). However, the majority of those who have dealt with the chemical



fractionation of pituitary extracts agree that follicle stimulation and tubular growth in the testis are mainly controlled by one hormone (FSH) while luteinization and interstitial cell maintenance are a property of a second factor LH (or ICSH). Progress in the purification of these two hormones has been reported from several laboratories (37 to 41).

Follicle stimulating hormone has been prepared virtually free of other hormones (37 to 42), while two laboratories have succeeded in preparing luteinizing hormone in a pure form from swine (43) and sheep (44, 45) hypophyses so that it behaves chemically as a single protein entity. The two pure preparations of LH differ, however, in electrophoretic mobility and in other respects; that from swine pituitaries has an isoelectric point at pH 7.45 while that of the sheep preparation is pH 4.6 to 4.8. A comparison of the several methods of preparing LH indicates that there is lack of agreement in different laboratories as to the physical properties of the hormone. The recent development of a sensitive, accurate, and specific assay method for the hormone (46) should facilitate further work and clarify the existing confusion. It has recently been suggested (47) that the current designations FSH and LH (ICSH) be changed to the terms "Thylakentrin" and "Metakentrin" respectively, but the advisability of this departure has not gone unquestioned (48).

*Environmental influences.*—The reproductive cycles of vertebrate animals, while primarily under the control of the endocrine system, are greatly influenced by the external environment. The importance of environmental factors is indicated by the close correlation of reproductive function in many animals with the seasons of the year. The length of day and night, the exposure to artificial light and darkness, and temperature are known to have important influences on the regularity of the estrous cycle and sexual behavior. There is an extensive literature dealing with various aspects of this subject but it is possible to mention only a few of the more recent investigations.

Since the earlier investigations of Rowan (49) and Bissonnette (50) on the effects of light on reproductive activity in birds, similar experiments have been conducted on many species of vertebrates. One of the important general observations made is that all animals do not respond equally well to light. While in most species an artificially lengthened day advances the breeding season, in others,



such as the rabbit, guinea pig, hedgehog, and ground squirrel, such treatment so far has failed to show any definite effect. In the ground squirrel, temperature seems to be more important than light (51). Most animals come into a breeding condition while the light treatment is in progress, while in others corresponding reactions are elicited by shortening the day following a period in which the day was lengthened (52). Bissonnette (53) found that the breeding cycles in goats are controlled by light in such a way that short days induce breeding cycles while long days inhibit them.

Browman (54) found that rats subjected to constant light had long periods of vaginal cornification ranging from a few days to several weeks. Also young rats from which the eyes had been removed at birth showed delay in sexual maturity. Fiske (55) found that immature female rats kept in the light from birth or from the twenty-first day of life come into sexual maturity about six days earlier than normal and sixteen days earlier than those kept in darkness. Animals kept in constant light had unusually long periods of estrus and slightly lengthened periods of diestrus, while rats kept in darkness exhibited metestrous smears for many days. Fiske also found that the ovaries of rats in constant light became increasingly follicular and regressed in size as the duration of exposure to light increased, whereas ovaries of rats kept for a similar time in darkness were larger and fully functional. It was also concluded from the gonadotropic activity of the pituitaries that those of animals kept in the light contained more FSH and those in darkness more LH. It is also of interest that the pituitaries of such animals showed marked cytological modifications (56).

The influence of light on gonadal development apparently depends upon retinal stimulation and the effects of such stimulation upon the pituitary. The response elicited by light does not occur after hypophysectomy, and division of the optic nerves, or removal of the eyes, either prevents or greatly retards the reaction. Such observations indicate the existence of nervous connections between the eye and the pituitary. This supposition has been the basis of a number of morphological and physiological studies. Recently a series of experiments was devised by Clark, McKeown & Zuckerman (57) in order to discover possible nervous pathways through which retinal stimulation may affect the pituitary in



ferrets. They found that anestrus ferrets would respond normally to additional daily illumination in the absence of the anterior corpora quadrigemina, when all retinal impulses to any part of the midbrain had been interrupted, and when retinal impulses to the dorsal nucleus of the lateral geniculate body and the visual cortex had been completely interrupted. They also present evidence for thinking that a normal response can occur in the combined absence of the visual cortex and the anterior corpora quadrigemina or even after the interruption of retinal impulses passing to the dorsal nucleus of the lateral geniculate body, visual cortex, anterior corpora quadrigemina, and pretectal area. From these observations they suggest that the visual response depends on impulses passing either to the ventral nucleus of the lateral geniculate body, or to the subthalamus by way of the accessory optic tracts.

*Nervous influences.*—Section of the hypophyseal stalk induces changes in anterior pituitary function which vary with the species of the experimental animal and apparently also with the technique of operation used. In the rabbit this operation prevents ovulation following coitus but does not affect sexual receptivity (58). It does not materially disturb the vascular supply (59) but interrupts certain but not all nerve fibers to the anterior lobe (60). In rats a variety of changes have been described in stalk-sectioned animals (61) but in this species damage to the anterior lobe itself is frequent (62), and failing this, little influence is noted on the sexual cycle. A recent study failed to demonstrate any pituitary function in pituitaries which were transplanted to the eye (63). Appropriately placed hypothalamic lesions in guinea pigs result in variable effects on the cycle. In general three results may be found: (i) anestrus, (ii) prolonged estrous periods, (iii) no effect (64); the structure of the ovaries indicates that hypophyseal gonadotropic function is correspondingly disturbed (65). In the female guinea pig the sexual behavior is in keeping with the gross changes of the cycle, while in the male similar lesions induce sexual impotence without genital regression (66). In the light of earlier experiments (67), it is difficult to interpret the effects of these lesions on the estrous cycle and it has recently been pointed out that similar effects are observed under many experimental conditions which are detrimental to the animals' well-being, such as resection of the kidney (68). Although hypophysectomy abolishes heat behavior



from sex hormone administration in the guinea pig (69), this operation does not influence the heat response of the rat (70, 71) to estrogen and progesterone.

Most that we know about the physiology of reproduction in the vertebrates has come from a study of mammals and we have become accustomed, consciously or unconsciously, to thinking in terms applicable only to that group of animals. This in some respects is unfortunate as it has probably distorted our view of the vertebrates as a whole. For example, we customarily think of spontaneous ovulation as being the rule and ovulation depending upon the nervous stimulation of mating as the exception. One should not be surprised if it is found that from the standpoint of number of instances the true situation is the reverse. Ovulation in many birds and cold-blooded vertebrates is the culminating event of a more or less complicated series of love antics. It is quite probable that these sexual displays have a direct bearing upon ovulation and that in many species ovulation would not occur in the absence of such sexual experiences.

#### SEX HORMONE METABOLISM

*Estrogens.*—It is now generally agreed that the estrogenic activity of human pregnancy urine may be attributed largely to its content of estriol, estrone, and estradiol (72, 73); recently a fourth estrogen has been detected which is nonketonic and neutral (74), and it is of interest that estradiol has been isolated from the human placenta (75). The nature of the compounds responsible for the estrogenic activity of the urine of nonpregnant human beings has not been determined but it has been generally assumed that these same substances are present. Wide variations are reported for the normal pattern of estrogen excretion during the menstrual cycle. The double peak of excretion, one in mid-cycle and one toward the end of the luteal phase, has in general been confirmed (76, 77, 78, 79). It has been suggested that the height of the second peak is related to the degree of function of the corpus luteum, but there is considerable individual variation. Such may be anticipated from the observations of estrogen excretion in men and in women after the menopause. The quantity of estrogen from some extraovarian source may be sufficient to account for the difficulties in interpreting the cyclic changes in women. Estrogen values are reported to



be low in cases of functional uterine hemorrhage (80), to show an annual cycle in normal women (81), to be high in women with cancer (82), and to show no increase in Cushing's syndrome (83). The proportion of urinary estrogen detected in the free form was higher than normal during menstruation and during periods of abnormal uterine hemorrhage (84).

During pregnancy the greatly elevated estrogen levels follow roughly the levels of pregnanediol excretion. The highest levels of excretion are noted one to three weeks before term, and labor occurs during a period when the estrogen level is falling (85, 86). In cases of toxemia of pregnancy, the estrogen levels are said to be low (87, 88, 89), but in one case very high values were found (86).

Heretofore biological methods have been preferred for the assay of urinary estrogens from nonpregnant individuals. A chemical method has been proposed whereby the estrone fraction can be quantitated; it is based upon the color produced when the ketonic, weakly phenolic fraction is coupled with diazotized dianisidine (90). The large amounts of estrogen in pregnancy urine lend themselves more easily to chemical quantitation and a new method has been developed whereby either total estrogen or the various components thereof can be determined (91). This method carries an accuracy of  $\pm 10$  per cent when applied to urine from the last two thirds of pregnancy. A sensitive color reaction for pure estrogens has been developed based upon a chloroform-soluble compound formed by a reaction with phthalic anhydride. As little as  $0.25\mu\text{g}$ . estrone can be detected (92). Stilbestrol in urine has been measured by a color reaction with antimony pentachloride (93). The observations that large doses of testosterone propionate increase the estrogen titer of the urine of normal men (94) and eunuchs (95), lend support to the theory that at least a part of the estrogen in male urine takes origin from a degradation of endogenous androgen (95). However, only a part of the urinary estrogen from males can be ascribed to this source, for the urine of eunuchs contains estrogen, and considerable amounts of estrogenic activity are to be found in the urine of women after oöphorectomy (96). Nor can the adrenals be the sole source of extraovarian estrogen for in cases of Addison's disease the estrogen excretion in both sexes was considerable (96).

Species differences in the metabolism of steroid hormones are striking, and results from one species are difficult to transfer to



another. This is well demonstrated in the case of pregnanediol and androgen excretion, but is less striking with the estrogens. In the female chimpanzee, two peaks of estrogen excretion were observed corresponding to those of the human menstrual cycle. The male excreted somewhat less estrogenic material than the female (97). Estradiol dipropionate injected into guinea pigs caused the appearance of estrone in the urine which was identified by its isolation as the benzoate (98). In dogs, only a small proportion of injected estrogen could be recovered in the urine when calculated on an activity basis (99). The recovery in the urine of rabbits of substances related to the estrogens following the administration of a series of stilbene derivatives has been studied in detail (100, 101). It is quite clear that only a small fraction of injected estrogen appears in the urine in the form of physiologically active compounds. Furthermore as a considerable proportion of the normal urinary estrogen arises from some extraovarian sources its determination is of doubtful diagnostic value in nonpregnant women.

*Corpus luteum hormone.*—Numerous measurements on normal human female urine confirm that during the latter half of the cycle, sodium pregnanediol glucuronidate may be recovered in amounts of 1 to 10 mg. daily (102, 103, 104), and the presence or absence of this substance correlates well with the finding of a progestational or a follicular endometrium respectively (105, 106). Thus there remains little doubt that pregnanediol represents a major excretion product of the corpus luteum hormone in the human being. However, the recovery of the pregnanediol complex after the injection of progesterone has been the subject of less consistent reports. In cases of functional uterine bleeding wherein no evidence of corpus luteum function or of pregnanediol excretion exists, the injection of 5 mg. progesterone daily for ten days only occasionally resulted in a detectable amount of the pregnanediol complex in the urine, even though this amount of progesterone induced endometrial changes (107), and in certain other menstrual disturbances no pregnanediol could be found after treatment with progesterone (108, 109). It has been shown that the amount of pregnanediol complex recovered after the injection of progesterone varies with the sexual status of the individual; recovery was greatest during periods when the complex was already being excreted, when it may amount to 55 per cent, and least in cases of decreased ovarian function. When small amounts of progesterone are given at times



when a corpus luteum is absent, recovery may be zero, with most figures falling between 5 and 15 per cent (110). The uterus is unessential to the reduction of progesterone to pregnanediol, for women with functional corpora lutea excreted pregnanediol after hysterectomy and recoveries of pregnanediol after the injection of progesterone were as great after hysterectomy as before (111). Furthermore progesterone injections into men resulted in pregnanediol excretion (112, 113). With the possible exception of desoxycorticosterone (114), no substance other than progesterone has been shown to be converted into pregnanediol glucuronidate in the human being. Pregneninolone in doses of 160 mg. daily for fourteen days had no effect on pregnanediol excretion (115) while desoxycorticosterone acetate under similar circumstances had little effect (116).

Large doses of estrogen given during the latter half of the menstrual cycle in normal women decrease the quantity of pregnanediol complex excreted (117) while smaller doses earlier in the cycle are without effect (118). Likewise, testosterone propionate in four to five daily doses of 25 mg. each did not influence the level of subsequent pregnanediol excretion (119). When free pregnanediol is administered it may be recovered in the urine as sodium pregnanediol glucuronidate in yields of from 0 to 100 per cent when given orally to men (120). None was recovered after hypodermic injection (110). When sodium pregnanediol glucuronidate is given by either route about one half can be recovered unchanged in the urine (110, 120).

An interpretation of the recorded results of pregnanediol excretion in nonpregnant individuals becomes clearer when cognizance is taken of the difficulty of making accurate quantitative determinations of sodium pregnanediol glucuronidate. That the current method is not uniformly accurate is attested by the numerous attempts to introduce minor modifications of the method (102, 121, 122). When small amounts are isolated, no certainty can be adduced as to the identity of the substance in question (110). A greater difficulty is the spontaneous hydrolysis of the complex that occurs in the interval between excretion and extraction. This hydrolysis cannot be prevented by preservatives and necessitates the recovery of the resulting free fraction which must be added to the combined portion to give the total (123). These difficulties can be largely overcome by hydrolyzing the urine before extraction



and determining the free pregnanediol (124). When this is done, pregnanediol may be determined by a colorimetric procedure on the same sample that is used for 17-ketosteroids (125).

Small amounts of pregnanediol are excreted in the absence of the ovaries. Amounts of less than 1 mg. per l. have been isolated from the urine of normal men (126) and from the urine of oöphorectomized women (127). Such quantities are not detectable by the usual quantitative clinical methods.

After the third month of pregnancy there is a marked increase in the excretion of pregnanediol and, during the last trimester, monthly cycles of excretion are to be observed (86, 128); labor sets in during a period when the pregnanediol excretion is falling rapidly (85, 129), and by the fifth day postpartum excretion ceases completely. Studies during late pregnancy will be greatly facilitated by the recent demonstration that pregnanediol excretion is continuous and steady during the twenty-four hours so that twelve hour or eight hour specimens may be used instead of the more difficultly collected twenty-four hour amounts (130). In the toxemias of pregnancy, Cope (131, 132) found that pregnanediol excretion is not materially reduced while Smith & Smith (87) observed a marked reduction. It has recently been shown that low levels are to be found only in those cases of toxemia in which albuminuria occurs (133). The pregnanediol excretion during pregnancy following the complete removal of all ovarian tissue was found to be consistently lower than the minimal normal range (134). The operation was performed on the sixty-third day after the last menstrual period. Chorionic gonadotropin assays were normal throughout and no untoward effects on the gestation or on parturition were observed.

Further attempts to obtain pregnanediol from the urine of animals other than the human being have been unsuccessful. None was found in the urine of pregnant monkeys (135), chimpanzee (136), cat, dog, or rabbit (137). No pregnanediol was found in a case of Hans Schuler Christian disease (138) and low values were reported in cases of cystic disease of the breast (139). In a case of suspected adrenal cortical hyperplasia large quantities were excreted (140) and the diagnostic importance of this finding had already been pointed out (141).

Assays have been made of human (142) and monkey (143) blood for progesterone-like substances during the normal men-



strual cycle, the sensitive test devised by McGinty *et al.* (144) being employed. The results of this promising technique are not entirely consistent with current views of the periodic secretion of corpus luteum hormone, but they suggest that with the improvement of quantitative assay methods more exact data will be obtained.

*Androgens.*—A number of modifications and refinements of the Zimmerman color reaction for urinary ketones have been proposed (145, 146, 147, 148). Further fractionation of the neutral extract of acid-hydrolyzed urine permits the separation of ketonic lipids into alcoholic and nonalcoholic portions and the former into alpha and beta alcoholic fractions. These separate fractions have been determined colorimetrically (149, 150, 151, 152) or assayed biologically (153). When such purifications are performed it appears reasonable to attribute the major portion of the resulting color to 17-ketosteroids. However, similar colors may result from many ketonic substances and, unless spectral analysis is applied, no certainty is afforded that the chromogen is a sterol (154, 155, 156). Consequently, one may sometimes reasonably doubt the identity of the substances in question when no purification is carried out and when no data are given on the quality of the resulting color.

The relationship between substances studied by these colorimetric methods and the androgenic potency of urinary extracts as tested biologically is still a question of some uncertainty. Although a certain degree of parallelism exists between "17-ketosteroid" excretion and "androgen" excretion, notable exceptions occur, especially in urines from abnormal cases. This lack of parallelism is not surprising when one considers that the several urinary androgens are of different biological potency and that some of their excretion products are biologically inactive.

It is becoming increasingly apparent that the quantities of androgen or of 17-ketosteroid excretion are measures less of testis endocrine function than of the activity of the adrenal cortex (96). It has been estimated that the human male excretes about 9 mg. of 17-ketosteroid daily, while the human female level is about 6 mg. Castration in the male reduces the 17-ketosteroid excretion to the female level, while a total loss of adrenal cortical function as in Addison's disease decreases the level in both sexes to near zero. Consequently, the approximation has been made (157) that of the average total daily excretion of 17-ketosteroids of 9 mg., 6 mg. in



either sex takes origin in the adrenal cortex, while 3 mg. derives from the testes and none from the ovary. However, the finding that certain normal women show a large excretion of  $\beta$ -alcoholic 17-ketosteroids in mid-cycle would seem to suggest an ovarian, perhaps a corpus luteum, origin for some of the total (158). Other studies have not shown a periodic secretion of total 17-ketosteroids during the cycle either in the human being (76) or chimpanzee (97).

Several reports concur on the greatly increased excretion of 17-ketosteroids in cases of masculinizing adrenal cortical tumors, values as high as 176 and 166 mg. daily being recorded (157, 159, 160). In Cushing's syndrome no such increase occurs (160, 161) and 17-ketosteroid values may be below normal. Thus a difference of diagnostic importance between these two similar conditions is manifest. Furthermore, in a case of masculinization caused by an arrhenoblastoma of the ovary, the androgen titer of the urine was only slightly increased (162).

It has been suggested that of the several compounds giving the Zimmerman reaction *trans*-dehydroandrosterone derives chiefly from the adrenal cortex, while androsterone and its biologically inactive isomer etioallocholan-3( $\beta$ )-ol-17-one may be the excretion products of testosterone derived from the testis (153, 163, 164). Thus eunuch urine was found to contain one half to one third the normal content of androsterone and etioallocholanolone but ten times the normal amount of *trans*-dehydroandrosterone (165). In a case of adrenal tumor in a woman, the latter substance was excreted in amounts one hundred times normal (166). Injected testosterone, however, appeared in the urine mainly as androsterone and its isomer. Androsterone was isolated from the urine after the oral administration of androsterone, etioallocholan-3( $\alpha$ )-17-diol, etiocholen-(4,5)-3,17-dione and etioallocholan-3,17-dione, a finding which suggests that one or more of these substances are intermediates in the normal conversion of testosterone to androsterone and etioallocholan-3,17-dione (153).

Whether or not dehydroandrosterone can result from a conversion of testosterone in the body has been debated (166, 167, 168). The fact that a large portion of injected testosterone can be recovered as androsterone (a relatively active androgen) may explain the finding of a higher androgen to 17-ketosteroid ratio after injecting testosterone than is found in normal urine (155).

It has been found also that large amounts of 3- $\beta$ -ketosteroid



are present in urine from patients with adrenal tumors (160), and this suggests that this fraction takes its major origin normally from products secreted by the adrenal cortex. However, etiocholan-3( $\alpha$ )-ol-17-one was isolated from a case of virilism in a female (169); the beta form of this compound was isolated from normal urine (170) and as an excretion product of injected testosterone propionate (163, 164).

When testosterone propionate is given by mouth on an empty stomach, a rapid urinary excretion of androgen takes place. Within an hour androgen is detectable in the urine and by twelve hours the major excretion is complete. A single intramuscular injection induces a slower increase in urinary androgen which then persists for several days, the major excretion occurring during the first twenty-four hours. Pellets of testosterone propionate induce a prolonged elevated urinary androgen excretion. The biological effect is in inverse proportion, being least after oral administration when excretion is greatest (171).

Young children excrete only small quantities of 17-ketosteroid and the quantity excreted parallels somatic development in both sexes (160, 172, 173, 174). A close correlation was found between 17-ketosteroid excretion and creatinuria, a fact suggesting that the former also is correlated with muscular development (175). The ketosteroid excretion in women is decreased during estrogen administration (176) and during periods of pathological uterine bleeding (177).

#### PHYSIOLOGICAL EFFECTS OF SEX HORMONES

*Estrogens.*—A great many papers have dealt with the physiological, pathological, and clinical effects of natural and synthetic estrogens. Many of these confirm and extend earlier work while a minority advance our knowledge of the mechanisms of estrogen action.

Estrogens have been shown to exert a direct action, or at least one not involving the hypophysis, upon the ovaries of rats. Relatively large doses of various estrogens induce an increase in the weight of the infantile ovaries of hypophysectomized rats, an effect attributable to the development of many small follicles. Still more striking is the greatly increased response of such estrogen-treated ovaries to human and equine chorionic gonadotropin (178, 179, 180). This augmentation of chorionic gonadotropin is



similar to that commonly observed with pituitary extracts and variously attributed to a specific pituitary synergist or to follicle stimulating hormone. In intact rats large doses of estrogen reduced the ovarian response to human chorionic gonadotropin (181). It will be recalled that earlier work demonstrated that estrogen exerts a maintaining influence upon the corpora lutea of rabbits, an action which in this species is independent of the hypophysis. This has recently been confirmed (182, 183) in the hypophysectomized and hysterectomized animal, and a similar effect has been claimed in the human being (184). The question of whether these two apparently direct actions of an ovarian hormone on ovarian structures represent a physiological process or merely an interesting pharmacodynamic effect must await further investigation. In the adult rat, estrogen induces a period of active corpus luteum function (185, 186, 187), but in this species the effect is clearly mediated by the anterior pituitary (13).

Further work has been done on the mechanism of estrogen action upon the uterus. The production of an acetylcholine-like substance by estrogen-stimulated uteri of rabbits has been confirmed, but no such substance was found in the uteri of cats or rats after the injection of estrogen (188, 189, 190). Data supporting the concept that estrogen action upon the uterus is a cholinergic one have been presented (191). This work attempts to show that the vascular and growth effects of estrogen can be differentiated, while the consensus of present opinion supports the concept that these two phenomena are intimately related. The serum of the adult female rat and mouse contains more cholinesterase than that of the male (192), while estrogen is said to increase the level of liver cholinesterase in male rats to the high level found in females (193, 194). In the rat, however, the uterine response to estrogen is not potentiated by physostigmine, prostigmine, or pilocarpine and is not specifically inhibited by atropine (195); moreover, acetylcholine does not exert a vasodilator action (196). Further data must be accumulated before this aspect of estrogen action is settled, but at present it does not seem likely that acetylcholine is essential to the normal physiological action of estrogen upon specific tissues. The assumption having been made that uterine vascularity is controlled by cholinergic impulses, prostigmine has been advocated as a therapeutic and diagnostic measure in delayed menstruation in human beings (197). This drug is said to precipi-



tate bleeding in those cases of delayed menses in otherwise normal individuals provided pregnancy does not exist. Obviously such a phenomenon is open to several interpretations and, as such apparent therapeutic results in this condition are not new to gynecologists, there is not complete accord in the matter (198, 199, 200). An interesting technique has been applied to the study of the early hydration effect of estrogen upon the uterus, involving the injection of trypan blue one-half hour prior to autopsy. In the castrated rat or rabbit little staining of the uterus takes place while within three hours after a single injection of estrogen the uterus is deeply infiltrated with the dye. Thus the early accumulation of water in the uterus is apparently secondary to vascular changes involving an increased capillary permeability (201).

The influence of large doses of estrogen on carbohydrate metabolism has not yet become entirely clear. Large doses have been found to increase the blood sugar and liver glycogen under certain conditions (202, 203, 204) and to cause an aggravation of experimental diabetes in pancreatectomized ferrets (205). These results are in opposition to earlier reports of the beneficial effects of estrogens on experimental and clinical diabetes; but recent reports also claim that estrogen decreases the insulin requirement of diabetics (206) and that estrogen and progesterone induced a marked improvement in a type of diabetes associated with the menopause (207). It has been found that in intact rats the insulin content of the pancreas is increased by estrogen (208). Although these reports are not entirely in harmony, many workers recognize that the adrenal cortex is enlarged by estrogen, and that prolonged high dosages depress hypophyseal function and in some species such as rats induce adenomatous growths of the pituitary with consequent functional hypophysectomy (209 to 213). Either of these effects would profoundly alter carbohydrate metabolism and under different conditions may give diametrically opposed results.

Estrogen treatment will also cause a decrease in oxygen consumption in rats (214, 215), perhaps through similar indirect mechanisms, but was found not to influence oxygen consumption or the respiratory quotient in human beings in doses of 250,000 I.U. (216).

Brief mention should be made of certain miscellaneous effects produced by estrogen. Large doses increase the density and ash content of growing bone (217, 218) while physiological doses have



no effect (219). It has been found beneficial in the treatment of menopausal osteoporosis (220, 221). It produces a profound atrophy of the genitalia of male rats (222) and rabbits, an effect which renders the latter species less susceptible to experimental syphilis (223, 224); it increases the motility of the human uterus (225, 226, 227) and that of the rabbit (228) and cat (229). It increases the incidence of "takes" in endometrial transplants in rabbits (230); it causes an endometrial hyperplasia in monkeys (231); it induces demasculinization in cases of female virilism (232) and gynecomastia in males (233); it increases the activity of senile male rats (234); it inhibits ovulation in human beings with a consequent relief of essential dysmenorrhea (235) and in rabbits after cervical stimulation (236); it causes increased frequency of urination in the human female (237), a decrease in fluid intake in rats (238); it increases water retention in monkeys (239), in human beings (240), and in frogs (241); it causes a dilatation of skin capillaries in human beings (242) and inhibits hair growth in dogs (243).

*Stilbestrol* ( $\alpha,\alpha'$ -diethyl-4,4'-stilbenediol).—Since the discovery of the remarkable estrogenic activity of this substance in 1938, its properties have been tested by nearly all available criteria and found not to differ qualitatively from the known natural mammalian estrogens. Its use as experimental material has been so widespread since its discovery that in less than three years it was possible to cite two hundred and fifty-seven papers on the subject (244).

The similarity in the physiological action of this compound and estradiol has been explained on the basis of a similarity in spatial configuration of the two compounds (245) and it has been pointed out that the molecular size and empirical formulae of the two classes of substances are very similar (246). A similar substance, hexestrol (*p,p'*-1,2-diethylethylene diphenol), has very similar properties but has not been as widely used though it is readily synthesized from dianisylhexane (247).

The clinical use of stilbestrol has been attended by the observation of numerous toxic manifestations. The most frequent untoward symptoms are nausea, vomiting, anorexia, and abdominal or pelvic discomfort. Other symptoms include headache, vertigo, mental depression, drowsiness, diarrhea, and skin eruptions (248 to 258).



Several workers have found that toxic manifestations are related to high dosage (252, 253, 254, 256, 259, 260), while some have claimed that almost any dose in excess of 0.1 mg. daily may induce nausea in some patients while other individuals have no unpleasant symptoms from large doses (250, 255). Hexestrol is said to be less toxic (261) but equally active (262).

Of great interest is the observation that pregnant and lactating women have no toxic reactions even from massive dosages of stilbestrol (263, 264, 265, 266). Although the reason for this phenomenon is not clear, it seems that a part at least of the toxicity of stilbestrol may be related to its physiologic potency, and to the fact that the dosages given are actually higher in unitage than was at first realized. In the first place, stilbestrol is not as readily destroyed by the liver as are the naturally occurring estrogens and a larger percentage appears unchanged in the urine of rats (267), rabbits (100, 101), and human beings (253). As a consequence of its greater stability in the body, it probably exerts a more prolonged action than the free forms of the steroidal hormones. Thus after a single dose of only 1.0 mg. the urinary titer of estrogen remained elevated for from three to five days (253), while after a single injection of 1.0 mg. for each ten pounds of body weight, a marked elevation of urinary estrogen level occurred which had not returned to normal at the end of ten days (257). A single large dose in rats will maintain estrus for as long as two weeks (268). Experimental work has heretofore been based on the concept that the potency of stilbestrol was intermediate between that of estrone and estradiol. Now should stilbestrol have a more prolonged action than these natural estrogens, the effectiveness of repeated doses would be considerably higher owing to a cumulative effect. A recent study (269, 270) bears out this impression. When assayed on immature rats by a divided dose technique over three days, the effectiveness of stilbestrol upon the uterus and the vagina was found to be four times that of estradiol and sixteen and forty times that of estrone and estriol respectively. When given by mouth, stilbestrol was as effective as an equal dose of estradiol given subcutaneously. Should the potency of stilbestrol be of this order the usual clinical dosages will have to be revised downward. Toxic reactions may then be expected to become less troublesome.

The most striking toxic effect of stilbestrol is upon the hemopoietic apparatus of dogs. Recent studies on this phenomenon



(271, 272, 273) show that the formation of all blood elements is affected so that a picture resembling aplastic anemia results. This effect was first observed with the natural estrogens and derivatives thereof; stilbestrol is not more toxic in this respect (274, 275). Other animals that have been investigated have failed to exhibit this response; massive doses in monkeys (276), rats (210), and human beings (240, 257) did not materially influence the formed elements of the blood in most cases. In the human being hemoglobin and erythrocyte counts may actually be increased (248). Liver damage is said to occur in animals given massive doses (210, 271, 277, 278, 279, 280), but numerous investigations have failed to detect any change in liver function or structure (249, 252, 257, 281). The possibility has been suggested that at least in dogs the minor liver changes may be secondary to the profound anemia (273).

*Progesterone.*—Two methods have been devised for detecting very small amounts of this substance. One is based on the local action of the hormone upon the uterine mucosa of the rabbit when placed in a segment of the uterine lumen (282, 283), the other on its inhibitory action upon estrogen-induced distention of the uterus of the rat (284, 285). Both of these reactions exhibit the peculiar phenomenon that only a certain dosage range is effective; above or below this rather restricted range the progesterone has no effect. In another study progesterone was found to inhibit the action of small doses of estrogen on the uterus of the mouse and to augment it in the rat (286). Without pretreatment with estrogen, moderate or large doses of progesterone can exert a full progestational effect in rats (287, 288, 289) while large doses in rats and guinea pigs will inhibit the pathological uterine changes induced by estrogen (290, 291).

The use of progesterone in the treatment of habitual abortion in women continues to receive support. Success has been reported (292, 293, 294, 295) with dosages of 0.5 to 5.0 mg. twice weekly. Judging from other studies dealing with pregnanediol excretion, progesterone production during pregnancy is comparatively enormous and it is difficult to see how such small doses so infrequently given could have a beneficial effect especially as no evidence exists that these cases of abortion are caused by a lack of corpus luteum hormone. In rats, 1 to 2 mg. daily is required to maintain preg-



nancy after oöphorectomy on the fourth day (296), and in the rabbit 5 mg. daily are necessary (297).

Clinical practice has indicated a beneficial effect of progesterone on endometrial hyperplasia and functional uterine bleeding (107, 295, 298). Progesterone also is said to be effective in controlling essential dysmenorrhea (299, 300), but the mechanism of this effect is obscure, for as recently pointed out (301, 302) uterine contractility in the human being, unlike that of the rabbit, is intensified by the action of corpus luteum hormone. Chronic cystic disease of the human mammary gland is said to be benefited by progesterone injections, a form of treatment suggested by the low levels of pregnanediol excretion in such individuals (303).

Progesterone injections during the normal human menstrual cycle were followed by withdrawal bleeding within seventy-two to one hundred hours provided the injections were given early in the cycle, presumably before ovulation (304). A total dose of 50 mg. over periods of two or five days was effective in all cases. When a brief treatment is given between the eighth and eleventh days of the cycle the period is prolonged or shortened, the effect depending partially upon the dose. Thirty milligrams was uniformly followed by bleeding within seventy-two to ninety-six hours while with smaller doses this did not occur but in some cases the next menstruation was delayed. Presumably the latter effect is one concerned with the inhibition or delay of ovulation (305). In the baboon, progesterone treatment early in the cycle resulted in ovarian regression (306). The inhibition of ovulation in the guinea pig by progesterone has been confirmed (307, 308); this hormone is also said to depress the gonadotropic content of the pituitary of the rat (309) and to decrease the urinary excretion of gonadotropin by menopausal women (310). In rats in constant estrous progesterone restores a normal cycle and reinitiates ovulation (311).

Pregneninolone or ethynyl testosterone has been investigated as a possible orally administered substitute for progesterone, and it has been shown to possess several types of physiological action. It is slightly androgenic when tested on the capon's comb (312), but much more so on the genital tract of rats (313). It induces initial vaginal cornification and greatly enlarges the uterus of oöphorectomized rats (312, 313). Its progestational potency on the



uterine mucosa of rabbits is about one tenth that of progesterone (312), but unlike testosterone it effectively transforms the primate endometrium into a progestational condition and its withdrawal results in menstruation (314 to 318). Such actions require total doses as high as 500 to 600 mg. when given orally (319). It has been used with varying degrees of success in habitual abortion, menorrhagia, and dysmenorrhea (115, 302, 320 to 324). This substance is also similar to progesterone in its action on sexual receptivity in the guinea pig (325).

Progesterone and desoxycorticosterone are similar in chemical structure and show overlapping physiological activities. Progesterone rivals desoxycorticosterone in its ability to maintain life in adrenalectomized rats (326), mice (327), and cats (328), to influence sugar metabolism in ferrets (205), to modify electrolyte shifts in rats (329), to cause atrophy of the adrenal cortex when given in large doses in intact animals (330, 331), and to stimulate water excretion (332).

Correspondingly desoxycorticosterone has been shown to have progestational effects on the endometrium of rabbits (333 to 337), cats (338), and weasels (339), and upon the vagina, sexual skin, and mammary glands of monkeys (340). It also induces sexual receptivity in the guinea pig and exerts progesterone-like effects in the vagina of estrogen-treated rats (341).

*Androgens.*—Considerable interest centers around the effect of androgens on the testis as this constitutes a possible complication in their therapeutic use in the human being. The demonstration several years ago by Moore & Price that androgen administration in normal male animals depresses testis size and function was followed by the observation of Walsh, Cuyler & McCullagh that androgens prevent the testis atrophy consequent to hypophysectomy. This apparent paradox is understandable in view of recent work. It has been shown (342) that androgen therapy will maintain spermatogenesis after hypophysectomy in adult male rats and will initiate it in immature animals provided the age of thirty-four days has been reached prior to operation. This effect of androgen becomes less marked in younger animals suggesting that the pituitary is essential for the meiotic transition from primary to secondary spermatocytes. In addition to the influence of age, the effect of androgens in the intact animal depends upon the size of the dose. Small doses have been found to be depressive, as originally ob-



served, while large doses do not alter testis size (343, 344, 345, 346).

A recent study has shown that when uninjected animals are caged with litter mates receiving large doses, the small amount of androgen transferred by contact is sufficient to cause testis atrophy in the "untreated" animals and thus accentuate the apparent stimulating effect of the large doses in the treated individuals (346). These effects on the testis are centered predominantly upon the tubular elements which constitute the major factor in testis size; both large and small doses of androgen depress the interstitial tissue, an effect shared by large doses of progesterone, desoxycorticosterone, and estrogen (343). In man, recent investigators have agreed that testosterone derivatives consistently decrease the spermatozoan count of the ejaculate (347, 348) and spermatogenesis as determined by biopsy (349), while small doses are without effect on the percentage of abnormal forms of spermatozoa (350).

The metabolic effects incident to the injection of large doses of androgen in the human male are of interest. It has been confirmed that such treatment causes an increased rate of oxygen consumption (351, 352, 353, 354), a retention of water, sodium, potassium, chloride, nitrogen, and phosphorus, with a consequent gain in body weight (95, 354). Such effects were more marked in eunuchoids than in normal men. These results are interpreted as indicating a gain in total body protoplasm including an increased development of bodily musculature as well as muscular strength (355, 356, 357).

Hemoglobin levels and erythrocyte counts were either not affected (95), or moderately elevated (354), while sugar tolerance was decreased (358). The respiratory quotient is sometimes lowered (354), a fact suggesting an increased utilization of body fat.

Androgen treatment is said to increase (348) or not to affect (352) the rate of epiphysial union but to cause a greater rate of bone growth (359).

Despite the increased metabolic rate, serum cholesterol levels were not consistently altered either in man (360) or in the rabbit (361). Induced or spontaneous creatinuria is distinctly diminished in man and also in the monkey (362), rat (363), and rabbit (364), but the creatinuria in cases of muscular dystrophy is unaffected (365). Large doses of testosterone propionate caused a flushing of the skin in normal subjects, an effect inhibited by estrogens, while



the spontaneous flushing phenomena of menopausal women was abolished by testosterone (366). A greater blood supply to the skin and an increased supply of oxygenated blood in surface capillaries was demonstrated after testosterone therapy (367) and an increased skin temperature was noted (349). The relation of these phenomena to the appearance of acne in a certain percentage of androgen-treated individuals has been discussed at length (368). Comprehensive reviews of testis physiology (369, 370) and of the clinical use of androgens in testicular dysfunction (371) have recently appeared.

Androgens have been widely applied to the treatment of various gynecological conditions. The rationale of this therapy is apparently dependent upon two major actions. The first is a depressive effect on hypophyseal gonadotropic function resulting in a temporary ovarian atrophy and the second is a direct effect upon the endometrium inhibiting its regression and decreasing pathological bleeding. Several reviews cover the clinical aspects of this subject (372 to 376). In the rhesus monkey the inhibiting effect of androgen on estrogen- or progesterone-withdrawal bleeding has been confirmed (377, 378, 379). Although the mechanism of this effect is not clear, a similar process appears to operate in cases of functional uterine bleeding, a condition which responds promptly to androgen therapy (380, 381). With continued treatment the depressive action on hypophyseal gonadotropic function becomes manifest and amenorrhea and ovarian atrophy ensue.

It is claimed that testosterone propionate under certain conditions exerts a stimulating effect on the ovaries of intact female rats (382, 383), and as no such action is detectable in hypophysectomized animals (179), the effect is interpreted to be a result of initial hypophyseal stimulation. The dose of androgen is apparently important in this regard for while 0.5 mg. testosterone propionate daily does not inhibit ovulation in mice (384), a dose of 2 mg. daily completely abolishes ovulation in the rat (385). Profound ovarian atrophy has been the usual consequence of prolonged administration of androgen in females of several species.

When testosterone propionate in large doses is administered to female mice a considerable enlargement of the kidney takes place (386); this effect is said to have a salutary influence on the subsequently nephrectomized animal (387) and on animals poisoned with mercuric chloride (388). When estrogens and androgens are



given together a still greater renal enlargement occurs in mice (389) which is attributable to a tubular and renal capsule hypertrophy, and the latter effect has also been observed in rats (390, 391, 392). In normal mice, a certain proportion of the glomerular capsules show a parietal layer of cuboidal epithelium, males exhibiting a much higher proportion of this type than females (393). Castration in the male results in a decrease in this type of capsule to the female level while androgen treatment has the reverse effect and results also in the development of a hydronephrosis (394). In early pregnancy the male type of capsule predominates suggesting an "androgenic" action of the ovarian secretions at this time (395). Further studies have indicated that progesterone is androgenic in the rat (396, 397), suggesting that this and other observed androgenic phenomena attributable to the ovary may be mediated by the normal corpus luteum secretions.

#### MENSTRUATION

With the advancement of our knowledge of the menstrual cycle of primates it becomes more obvious that the physiological processes involved are basically the same as those regulating the estrous cycles of other mammals. The only difference, other than the phenomenon of heat, is the periodic bleeding of the primate uterus associated with necrosis and loss of endometrial tissue. Menstruation is the most conspicuous event in the cycle and as such is a convenient landmark from which time relationships of other cyclic changes in the female reproductive tract can be measured. However, for a better understanding of the menstrual cycle, the morphological and physiological variations in the endometrium previous to menstruation is of more importance than the fact that bleeding occurs.

This view is supported by the recent research of Markee (398) on intraocular transplants of endometrial tissue in rhesus monkeys. This technique makes it possible to follow with great accuracy both gross and microscopic changes in the transplant during the normal menstrual cycle. It was concluded from these observations that it is preferable to speak of menstruation as an event in the growth cycle of the endometrium rather than of endometrial growth as a phase in the menstrual cycle.

The growth cycles of intraocular transplants can be divided into four phases: (i) a period of rest, (ii) and (iii) a primary and



secondary period of growth and (iv) a period of regression. The period of rest is the interval between a preceding period of regression, which may include menstruation, and renewal of growth. The length of this period is extremely variable as growth may start immediately after regression or there may be a delay of as much as ten days. The primary growth period starts with the beginning of growth and ends shortly before the middle of the menstrual cycle at a point corresponding in general with ovulation. The secondary growth period lasts from the middle of the cycle to about five days before the onset of menstruation. The area of a transplant is usually doubled during the primary growth period and doubled again during the secondary period. A growth cycle in the endometrium is invariably terminated by a period of regression which may or may not include menstruation. Menstruation depends in large measure upon the extent of endometrial growth and the rapidity of the retrogressive process. In cycles having abnormally long intermenstrual intervals, one or more growth periods, each followed by a period of regression, may occur without menstruation. The morphological aspects of endometrial growth and menstruation have been described in detail by Markee (398) and ably reviewed by Bartelmez (399). The most important observation is the marked similarity between the endometria of ovulatory and anovulatory menstrual cycles. From the standpoint of reproduction an anovulatory cycle must be considered abortive but the endometrial modifications during the growth periods, regression, and bleeding differ only in degree from those of a cycle in which ovulation occurs. These observations on monkeys are applicable to the human being. Bartelmez (400) found many intermediate stages in human endometria between ovulatory and anovulatory cycles. The endometrium of an anovulatory cycle sometimes could not be distinguished from that of an ovulatory cycle. These facts make such terms as "follicular bleeding" and "pseudomenstruation" unjustifiable.

Although our knowledge of uterine morphology and physiology has been greatly advanced during the last few years the specific causes responsible for precipitating menstruation are not definitely known. The dependence of the uterus on ovarian function strongly suggests that the controlling mechanism is regulated by the action of estrogen and progesterone on the endometrium. It is generally conceded that estrogen is the primary factor responsible for endo-



metrial growth and that this effect is greatly augmented by the concurrent action of progesterone. Also, menstruation usually follows when a series of injections of estrogen is discontinued, and it may occur during the treatment if the dosage is not maintained above a certain level. It is equally well known that such bleeding can be inhibited by giving progesterone; once progesterone has produced its effects it becomes more difficult for estrogen alone to maintain the endometrium (401).

It has been found more recently that the introduction of a short series of injections of progesterone during chronic treatment with estrogen may precipitate menstruation (402). Uterine bleeding can be induced in monkeys on 1000 I.U. of estradiol daily by giving 1 mg. of progesterone in a single dose on or after the twenty-first day (403). Nine out of thirteen animals so treated began bleeding at an average time of 7.7 days following the injection of progesterone. That the bleeding was brought about by the progesterone seems beyond question as the amount of estrogen given was well above that required to maintain the endometrium indefinitely. The specific effects produced by progesterone which are responsible for the failure of estrogen to maintain the endometrium are unknown but it seems quite improbable that 1 mg. could induce any noticeable histological change. It appears more likely that the effects are of the nature of a physiological conditioning of the endometrium.

Another factor in experimental menstruation in monkeys is a progressive increase in sensitivity of the endometrium to a withdrawal of either estrogen or progesterone as the treatment is prolonged. When estrogen is given for one or two weeks and then discontinued, bleeding begins on an average of 9.2 days later (404). If, however, the treatment is continued for several weeks bleeding may occur within forty-eight hours after the last injection. It has also been found that at the end of fourteen days the injections of estrogen can be discontinued for four or five days without precipitating bleeding while if the injections are omitted on two successive days after the treatment has continued for several weeks bleeding usually occurs on an average of 2.37 days after the skipped period (403).

The endometrium of a monkey becomes fully sensitized to a withdrawal of progesterone when 0.5 to 1.0 mg. is given daily for ten days or longer following a brief treatment with estrogen.



Engle (404) finds that in such experiments bleeding occurs on an average of 2.9 days after the discontinuance of progesterone. Different degrees of sensitivity to the withdrawal of progesterone can be established during the course of a chronic treatment with estrogen by giving 1 mg. of progesterone daily for periods of one to five days. The elapsed time between the last injection of progesterone and bleeding was taken as a measure of sensitivity to progesterone withdrawal. It was found that the average delay before bleeding following five daily injections of progesterone was 3.5 days; that after a three day period was 4.2 days; that of a two day period was 5.4 days; and the average delay following a single injection was 7.7 days (403). These observations indicate that with proper conditioning the endometrium becomes equally sensitive to a withdrawal of estrogen as to a withdrawal of progesterone but with estrogen the process requires several weeks while with progesterone it is only a matter of days.

The specific cause responsible for precipitating uterine bleeding in the normal menstrual cycle is not definitely known but two theories based largely on experimental evidence have been suggested. They are generally referred to as the "estrogen deprivation theory" and the "progesterone deprivation theory." It is true, of course, that menstruation may be precipitated by the withdrawal of either estrogen or progesterone but the exact part each hormone plays in the process of endometrial regression and bleeding in the normal cycle is yet unknown.

The recent work of Venning & Browne (405) on the excretion of sodium pregnanediol glucuronidate is a valuable contribution toward a solution of the menstrual problem in that it furnishes a means for estimating luteal activity in the human menstrual cycle. Judging from the amount of this compound that is excreted in the urine there must be a wide variation in luteal secretion in different cycles. In some cycles the compound is absent or present in the urine in such small amounts that it cannot be detected. When present the total amount per cycle may vary from 3.0 mg. to 54.6 mg. and the duration of its excretion may vary from three to twelve days. Yet regardless of the quantity or the length of time over which it is excreted bleeding occurs from zero to three days following the disappearance of the compound from the urine. These facts may account for the wide morphological variation found in menstruating human endometria (399).



When progesterone is injected into a human being only a part of it is recovered in the urine as sodium pregnanediol glucuronide (108, 109, 110). This seems to indicate that while the presence of pregnanediol in the urine during the menstrual cycle may be an adequate measure of the duration of luteal activity, it is not an exact quantitative measure of the progesterone secreted. These observations also suggest that progesterone may be secreted in sufficient quantity to induce uterine bleeding without the appearance of pregnanediol in the urine. Browne precipitated menstruation in women by injecting four 5 mg. doses of progesterone while Hamblen and co-workers gave the same amount daily for seven to ten days and did not obtain significant excretion of pregnanediol. Also, Seegar (107) was able to induce endometrial transformation with ten daily doses of 5 mg. of progesterone without inducing a consistent appearance of pregnanediol in the urine.

There is indirect but nevertheless convincing evidence that the secretion of progesterone in guinea pigs, rats, and rabbits begins prior to ovulation (9). This is also probably true of primates as there are many instances of partially luteinized follicles mentioned in the literature. This possibility, the variability in morphology of menstruating endometria (399), the observations on intraocular transplants (398), and the fact that the threshold dose of progesterone for endometrial stimulation is below that for its excretion as pregnanediol make it seem unwise to conclude that the absence of ovulation in a menstrual cycle necessarily precludes the possibility of effective luteal action. It is quite probable that menstruation ordinarily is precipitated by the cessation of progesterone secretion either from a corpus luteum or an atretic follicle while bleeding brought on solely by the withdrawal of estrogen might be much less frequent than previously thought.

#### SEXUAL SKIN OF PRIMATES

The sexual skin of the perineal region of many primates shows cyclic changes in size and color correlated with events of the menstrual cycle (401). The development of the sexual skin varies widely among different species. In the common rhesus monkey it undergoes a progressive maturation during puberty and adolescence (406). The sexual skin of a young animal shows conspicuous cyclic development but with each succeeding menstrual cycle the



swelling tends to become less while the coloration becomes more intense and may show little change in the adult. In certain baboons, fluctuations of the sexual skin persist throughout reproductive life and this perineal structure becomes enormously enlarged during each menstrual cycle (407). At the height of the swellings the sexual skin may attain a volume of 3.6 to 5.0 liters and account for as much as 35 per cent of the animal's body weight as compared with about 2 per cent when it is shrunken (408).

The physiology of the sexual skin is of considerable importance as it not only is controlled by the ovarian hormones but the reactions of its tissues may in certain respects be similar to those occurring in the endometrium. Swelling begins soon after menstruation and reaches its maximum at about the middle of the cycle, after which deturgescence sets in and is completed shortly before the succeeding menstruation. The increase in bulk of the sexual skin is due almost entirely to the accumulation of extracellular fluid. Swelling is associated with increased thirst and relative oliguria. The shift of fluid to the sexual skin is controlled by so powerful a stimulus that the remainder of the animal loses weight to the extent of at least 1.2 kg. During deturgescence the condition is reversed. At such a time a baboon has been known not to drink for eleven consecutive days and during the seventeen days from the start of deturgescence to the next menstruation only 0.25 liter of liquid was imbibed (408).

Swelling of the sexual skin in castrated adolescent monkeys can be induced and maintained for at least several weeks by giving estrogen. Maximal development is attained within ten to fifteen days and a rapid loss of swelling begins soon after the injections of estrogen are discontinued. If after the sexual skin has reached its maximal size, progesterone is given concurrently with estrogen, deturgescence begins on about the fifth day and is complete by about the tenth day. Thus, the characteristic action of estrogen on the sexual skin can be prevented by giving progesterone (401).

The interaction of the ovarian hormones in this reaction can be brought out to a better advantage by introducing a short series of injections of progesterone during a chronic treatment with estrogen. The injection of 1 mg. of progesterone daily for one to five days, beginning on or after the twenty-first day of estrogen treatment, will produce wilting of the sexual skin. Deturgescence begins on about the fifth day and continues until about the tenth



(403), regardless of the number of days on which progesterone is given, even though the injections of estrogen are continued.

Perhaps the most significant feature of these experiments is that the effects of a 1 mg. dose of progesterone lasts for ten days or longer. It is improbable that progesterone remains in the body for so long a time. It seems more likely that it conditions the sexual skin in a way that renders it unresponsive to estrogen and that some ten days are required to recover the original physiological condition.

The results reported by Gillman and co-workers (407, 409, 410) for the baboon parallel those for the macaque with the exception that the monkey seems much more sensitive to progesterone. Gillman & Smyth (411) found that when 3 mg. or more of progesterone is given in a single injection during the follicular phase of a normal cycle the perineal swellings pass rapidly through deturgescence and reach a flabby resting condition within five to seven days. This dosage of progesterone produces wilting of the sexual skin without uterine bleeding but if 20 mg. is given bleeding usually occurs with the completion of deturgescence. In similar experiments on sexually immature and castrated baboons, it was found (403) that progesterone would induce involution of the sexual skin in the presence of a maintenance dosage of estrogen. It was also found that menstruation following such treatment was either "estrogen-like withdrawal bleeding" or "progesterone withdrawal bleeding" depending upon the amount of progesterone that was given.

We are of course quite ignorant of the exact nature of the effects produced by progesterone which are responsible for modifying the action of estrogen. However, the idea that progesterone suppresses or inhibits the action of estrogen may, in some respects, be misleading (402, 407). Emphasis should be placed on the effects of progesterone on the tissue rather than placed on any theoretical neutralizing effect on estrogenic action. These effects of progesterone seem to be of the nature of a conditioned refractoriness. This conditioning can occur in the absence or presence of estrogen and may persist for several days after progesterone presumably has been eliminated from the body.

The physiological and biochemical changes produced by progesterone are in several respects directly opposite to those brought about and maintained by estrogen (408, 409, 412, 413, 414). Con-



sequently, a physiological situation is established by progesterone in the tissues affected that is contrary to the normal action of estrogen. The endometrium apparently becomes progressively more refractory to estrogen as the progestational reaction proceeds until finally a point is attained at which the original condition, produced by estrogen, cannot be restored nor deterioration and bleeding prevented by estrogenic action. The action of estrogen on the endometrium of primates is not inhibited by progesterone (401, 415). Estrogen seems to serve in a minor role as a synergist to progesterone which dominates the reaction and becomes indispensable for the preservation of the endometrium. Consequently, it seems more logical to consider the bleeding that occurs in the presence of estrogen, following a short series of injections of progesterone, as due to the absence of progesterone. This is probably true of all menstrual cycles in which progesterone is secreted, which may occur in the absence of ovulation and be insufficient in duration and amount to produce conspicuous morphological changes in the endometrium or appear in the human being as urinary pregnanediol.

#### MAMMARY GLAND DEVELOPMENT AND LACTATION

The endocrine control of the development of the mammary gland and of lactation has been the subject of several recent and comprehensive reviews (416 to 422) and only certain limited aspects of current work need be discussed here. The question of the direct or indirect action of estrogen upon mammary development continues to be an open one, and a thorough discussion of the subject is to be found in the above mentioned papers. The fact has been well attested in human beings (423), mice (424), rabbits (425), and monkeys (426, 427), that estrogen applied locally to the mammary area can induce growth in the treated region or gland without influencing distant glands. This finding renders untenable the concept that the estrogen acts upon the mammary gland solely through the hypophysis which then in turn mediates this action of estrogen. Continued work (428) substantiates the earlier consensus that hypophysectomy limits the effectiveness of estrogen in mammary growth, but a recent study (429) has shown that in hypophysectomized mice a distinct but slight growth effect is obtainable with estrogen which is somewhat augmented by the simultaneous injection of progesterone or of desoxycorticosterone



acetate. There can be no doubt that the injections of certain pituitary extracts in gonadectomized animals result in growth of the mammary gland but there is controversy concerning the extent of this growth and of its physiological significance in normal mammary development.

Evidence supporting the concept that the pituitary hormone responsible for duct growth is a specific mammogen which unlike all other anterior pituitary hormones is fat soluble has recently been given (430, 431). However, an independent study was unable to show any duct growth effect of lipoid-soluble whole pituitary extracts in hypophysectomized rats. Under identical circumstances the nonlipoid fraction, or whole pituitary powder, induced distinct mammary development (432). Growth hormone preparation also induced a limited mammary development in hypophysectomized rats and when given with estrogen yielded a pronounced estrogen effect. The degree of growth only roughly paralleled body growth (433).

We are forced to the conclusion that, as both estrogen and pituitary extracts are capable of exerting a growth effect upon the mammary gland, the normal situation probably entails an action of both hormones. The estrogen stimulus is a direct one which is more fully and completely expressed in the presence of a normally functioning hypophysis. This is in accord with the view previously expressed (434) that hypophysectomy is not specific in its limitation of estrogen action and that other deleterious influences such as dietary insufficiency have a like effect. Starvation, however, does not explain the hypophysectomy effect, for forced feeding in hypophysectomized animals does not restore their mammary response to estrogen (428). Many factors are involved in normal growth processes and in the absence of one of these a normal stimulus may not elicit its characteristic response.

A question which cannot be answered at the present time concerns the normal mechanism of the development of the pregnancy effect, i.e., lobule-alveolar growth. Estrogen alone will induce this effect in certain species such as the guinea pig and goat, and partially in others such as the monkey and human being. However, in many species the estrogen effect is largely on the ducts and does not resemble the state seen in pregnancy in those cases. When the corpora lutea of intact rats, mice, and rabbits are caused to function by the injection of human chorionic gonadotropin or pituitary



extracts, the mammary glands undergo extensive lobular development and may become capable of secreting milk.

This phenomenon can be brought about in hypophysectomized rats injected with relatively crude pituitary extracts rich in luteotrophin (13). This action requires the presence of active corpora lutea, but the injection of quite large amounts of progesterone have no such action (434) or only a moderate one. Massive doses of progesterone (15 mg. daily) will induce some mammary development in oophorectomized rats (288, 289), but this is not of the degree which favorably compares with normal pregnancy or with the result of corpus luteum stimulation. In the mouse, a somewhat complex situation has been uncovered which suggests that either the corpus luteum or the placenta can induce this effect. Thus it was shown that under circumstances which prevent abortion, castration during pregnancy in mice permitted a continued mammary development (435); hypophysectomy was also without an inhibiting effect in the guinea pig (436) or mouse (437), provided living placental tissue survived. It has been widely observed that intact adult female rats respond to injected estrogen by complete lobular development of the mammary gland which is an accompaniment of an induced period of active corpus luteum function (187). In short it would appear that either active corpora lutea or a functioning placenta may induce complete lobular development, an action which is poorly mimicked by corpus luteum extracts or progesterone. The pituitary is essential to this corpus luteum effect, but not to the mammary development induced by the placenta.

Recently several papers have appeared supporting the contention that in the absence of corpus luteum or placental function, pituitary extracts can bring about a lobular development of the mammary gland (438, 439), and that the factor involved is not progesterone (440). Here again the question seems to be one of degree, and it is yet to be shown that such extracts can directly cause a complete pregnancy development rather than a trend in that direction. It has been suggested (416) that a part of the effect of hypophyseal extracts on mammary growth may be mediated by the intact adrenal cortex for at least one derivative, desoxycorticosterone acetate, of its contained hormones will exert such an action in the normal (441) but not hypophysectomized mouse (471), and



in the monkey (340). It has been known for some time that the adrenals contain estrogen (442) and may be stimulated to secrete a gynecogenic substance (443) under certain circumstances.

Before reviewing the recent literature on lactation we desire to express a viewpoint to serve as a basis of subsequent interpretation. "Prolactin" is the original designation for the hypophyseal factor concerned with crop-gland stimulation of the pigeon and the inference was apparent that this substance is also the controlling factor in mammalian lactation. Other terms were subsequently suggested including galactin, mammotropin, lactogen, or lactogenic hormone, the last being at present most widely used. All these terms carry the same implication as to mammary secretion as the original name even though the assay upon which potency is based is almost universally the response of the pigeon crop sac epithelium. The question to be raised concerns the extent to which the "lactogenic hormone" is concerned with lactation in mammals. There is agreement that hypophysectomy abolishes milk secretion and that some restoration of this defect is achieved by the injection of crude pituitary extracts. Under such circumstances, earlier work has shown that lactogenic hormone alone is incapable of restoring lactation, adrenotropic hormone or adrenal cortical extracts being necessary in addition. Now at the time when these experiments were done, the lactogenic preparations used probably already contained adrenotropic hormone, for the separation of these two factors is difficult and as yet has not been reported to be complete. The remixing of two partially fractionated preparations probably results in a mixture of several factors. Furthermore, not only hypophysectomy but also adrenalectomy inhibits lactation, and thyroidectomy causes considerable diminution in milk yield. Cortical extracts and thyroxine can greatly augment established lactation while the injection of prolactin has been shown to have very little, if any, effect. A fraction has been prepared from adrenal glands which is more potent than cortin in maintaining lactation in adrenalectomized rats. This substance is said to cause a stimulation of the crop glands of pigeons (444). In view of this substance's properties (solubility in ether and precipitability at an isoelectric point) one should hesitate to identify it with the pituitary lactogenic hormone. The conclusion seems inescapable that, although the pituitary is one of the essential factors in



lactation, it can hardly be said that the evidence is sufficient to justify the view that the lactogenic hormone is more than a contributory agent.

It has been shown that purified lactogenic preparations are capable of causing a marked enlargement of the intestine, liver, and kidney in pigeons and to promote appetite and general body growth (25). It has further been shown that similar preparations have distinct effects on carbohydrate metabolism (445) and these workers have suggested that such an effect may be more important to lactation than a direct action on the mammary epithelium. It is of interest to note, in this regard, that while cortin will maintain lactation after adrenalectomy, desoxycorticosterone acetate is without beneficial effect (446), a fact further suggesting that carbohydrate metabolism is a primary factor in lactation.

Evidence has recently been presented to show that the pituitary secretes a hormone separate and distinct from the FSH and LH which is responsible for corpus luteum function. It has been suggested that this factor is closely related to (13) or identical with (15, 16) the so-called lactogenic hormone. Should it be established that these two factors are indeed identical, question may fall on the direct action of the hormone on the mammary gland. In any case, both actions are expressed by any relatively pure preparation of either factor so that to date experiments on mammary development and lactation are to be interpreted with this in view. For example, it has been reported that lactation may be induced in normal female guinea pigs by the injection of pure lactogenic preparations (447). The striking phenomenon noted was that lactation resulted only if injections were begun prior to the fourth day after estrus and that the hormone was ineffective if begun between the fourth and sixteenth days of the cycle. It has also been recently reported (15, 16), that this pure lactogenic hormone is highly efficient in maintaining the functional efficiency of the corpora lutea of rats and the question may be asked as to what extent of the mammary effect in the guinea pig experiments was mediated by an increased and continued functioning of the corpora lutea.

Lactogenic hormone was shown several years ago to cause a completion of the pregnancy effect in the mammary glands of pseudopregnant rabbits (448), an effect which consisted largely



in an expansion of already formed alveoli by a secretion from the alveolar epithelium. This action was recently confirmed and it was shown that other pituitary fractions and thyrotropic hormone were much less effective (449).

Great advances have been made in the purification and characterization of the lactogenic hormone (450, 451, 452, 453). The substance is extracted by a method published in 1937 (448) and further purified by similar procedures until the active fraction has a potency of 30 I. U. per mg., three times that of the international standard. It behaves as a pure protein in solubility studies, and in the Tiselius electrophoresis apparatus and ultracentrifuge. The isoelectric point of material obtained from either sheep or beef glands is at pH 5.73 but the hormones from the two sources differ in their solubility in acid sodium chloride solutions. The molecular weight has been estimated to be from 25,000 to 26,500. Further physiological studies using this material will be awaited with interest.

Numerous clinical studies on the effects of hormones on lactation have been made. An extensive series of experiments, involving the injection of moderately large doses of lactogenic hormone during the puerperium in women, failed to show any significant increase in milk secretion (454) while similar injections in new born infants caused a slight increase in the size of the infants' mammary glands and a questionable increase in the secretion of witch's milk. Estrogens including stilbestrol and androgens have been widely used in lactating women. The effect of these agents on the mammary gland is twofold and a distinction is to be made between an inhibition of milk secretion and a salutary effect on the subjective symptom of engorgement (445). Several workers have found that two to three days' treatment with 5 to 20 mg. of stilbestrol daily will prevent the onset of lactation or inhibit lactation already established (456, 457, 458). However, this inhibition is not complete for it has been reported that as much as 1000 mg. did not altogether prevent the onset of lactation provided suckling was permitted, but the normal amount of milk production was delayed until several days after the stilbestrol was discontinued. A total of 50 to 500 mg. over one to four days was said to have no effect on established lactation (459). A recent extensive study has shown that 5 mg. of stilbestrol given daily



from the time of parturition caused a significant reduction in milk secretion, an effect which disappeared in two to five days after the last dose (266).

Testosterone propionate in doses of 5 to 25 mg. daily for several days is said to have a distinct (463, 464) or only slight (455, 460, 461) effect on established lactation, but to be similar to estrogens in relieving the sensation of engorgement when nursing is discontinued (455). Progesterone in doses of 5 mg. daily for five to six days inhibited lactation in six out of nine cases (462). The consensus of recent work would appear to be that large doses of estrogen or of testosterone will cause only a slight inhibition of lactation when nursing is continued and that the administration of these agents when nursing is discontinued may give a false impression of their inhibitory capacities owing to the relief offered in inhibiting engorgement. When nursing is discontinued milk production will quickly cease even though no hormone treatment is instituted.

These results are in accord with animal experiments. Large doses of estrogen inhibited lactation in rats without influencing mammary involution (465) and chorionic gonadotropin given simultaneously was found to increase this estrogen inhibition (466). Androsterone in doses of 0.2 mg. daily for fifteen days did not inhibit lactation in rats (467) and it has been claimed that small doses of estrogen actually increase the quantity and quality of the milk of cows (468).

Earlier work which claimed that the uterus and the sympathetic nervous system are intimately concerned in lactation has not been confirmed (469). When the uteri of rats were distended with paraffin at or shortly after parturition the animals were made ill and inattentive to their young; vigorous litters were able to obtain a normal amount of milk (470).

#### PLACENTAL HORMONES

One of the problems that confronted mammals in the evolution of viviparity was that of retaining embryos in the uterus for a time beyond the limits of the normal estrous cycle. In the Monotremata the situation seems to be one in which the eggs are retained in the reproductive tract for some eight days (in *Echidna*) and when laid contain embryos comparable in many respects to



those of the hen after about forty hours incubation. The immature young of the Marsupialia are the product of an exceedingly short gestation. In both Monotremata and Marsupialia the length of gestation is comparable to that of a pseudopregant period or normal luteal phase and there is some evidence that expulsion of the eggs and young is correlated with involution of the corpora lutea. Under such a situation it seems unnecessary to postulate that hormones other than those regulating the estrous cycle take part.

The physiology of the first few days of gestation is apparently the same in all mammals as it is fundamentally that of the estrous cycle; however, as gestation is prolonged, other and rather diverse controlling mechanisms appear. One of the most important of these adaptations is a specialization of the placenta as an endocrine organ. The nature of this specialization is in effect the taking over of certain pituitary and ovarian functions by the placenta. The secretion of gonadotropins, estrogens, and progesterone by the placenta has been described for several species (472, 473).

When the adoption of pituitary and gonadal functions by the placenta is considered from an evolutionary standpoint it seems reasonable to suppose that the process might have followed somewhat divergent paths in different mammalian groups. The evidence we have points toward this possibility. Placental gonadotropins have been found in the monkey, chimpanzee, human being, mare, and rat (474, 475). These substances, as obtained from the three groups of mammals represented, differ widely in their physiological properties.

The function of the gonadotropin of the rat placenta seems to be that of prolonging the secretory activity of the corpora lutea from about the tenth day of pregnancy until term. The stimulation of luteal secretion is the only effect known to be produced by this hormone. It does not produce growth of follicles or luteinization in the ovaries of sexually immature rats, nor can it repair the ovaries following hypophysectomy. There is also considerable indirect evidence that the placentae of mice and rabbits secrete similar gonadotropins (183, 472).

The placental gonadotropin of the mare appears in the blood between the thirty-seventh and forty-second day of pregnancy and reaches its highest concentration between the fiftieth and eightieth day and gradually diminishes until it is absent after



about the one hundred and eightieth day (473, 476). This hormone, when administered to laboratory animals, produces both follicular development and luteinization. The part it plays in gestation is not clear but it may be significant that its presence is correlated with the development and growth of numerous accessory corpora lutea. Its appearance in the blood corresponds approximately to the time of implantation of the blastocyst and it disappears about one hundred and fifty days before parturition. The physiological mechanism controlling the last one hundred and fifty days of gestation is unknown but it has been shown that ovariectomy during this time neither interrupts pregnancy nor decreases the amount of estrogen excreted in the urine. There is evidence showing that the estrogen is secreted by the fetal placenta (477), thus indicating adoption of ovarian function.

The period of gestation in man averages two hundred and sixty-seven days, in the chimpanzee two hundred and thirty-five days and in the rhesus monkey one hundred and sixty-five days; the time during which placental gonadotropic hormone is excreted in the urine also differs in length. The hormone appears in the urine of pregnant women within two weeks following ovulation and prior to the expected date of the first missed period. It reaches its highest concentration between about the sixtieth and seventieth day and soon afterwards falls rapidly to a low level which is maintained in most cases until parturition. In the chimpanzee it is present in the urine from the twenty-fifth or thirty-fifth day and disappears between the hundredth and one hundred and sixtieth day. Its presence in the blood serum of the monkey lasts only from the fourteenth to the thirtieth day after ovulation (478). That this represents a phylogenetic series may be questioned but the gonadotropins excreted in the three primate groups seem to possess the same physiological properties (474, 478).

This hormone, as obtained from the urine of pregnant women, has been studied more extensively than any other and has recently been highly purified and identified as a glycoprotein with a minimal molecular weight of 80,000 (479, 480, 481). Recent studies show that it may soon be possible to detect this substance chemically and thus facilitate the early diagnosis of pregnancy (482). Its principal effect on the mammalian ovary, with few exceptions, is one of luteinization (473). It does not produce follicular development in the atrophic ovaries of hypophysectomized rats, nor does



it stimulate follicular growth in the normal monkey or human being. In fact it is said to cause regression in the normal human ovary (483). However, it will postpone menstruation in women if administered during the luteal phase of the menstrual cycle (484). In such experiments, the progestational condition of the endometrium is maintained and luteal function is further indicated by the continued excretion of pregnanediol. These observations and others on laboratory animals suggest that the placental gonadotropin of the human being can stimulate the secretion of both estrogen and progesterone by the corpus luteum.

The physiological properties of the placental gonadotropins clearly differentiate them from the pituitary gonadotropic hormones. Evidence for thinking that they are secreted by the fetal chorion seems convincing and especially so in the human being. Seegar & Gey (485) found that tissue of full term and four-month placentae, chorionic tissue of ectopic pregnancies, and hydatidiform moles continued to elaborate the hormone in tissue cultures for two to six months. It is obvious that such gonadotropins are hormones of pregnancy, a point that has been emphasized by a number of investigators. It has been proposed (486) that the generic term cyonin be applied to these hormones to signify their common tissue source and homologous function and at the same time correct the loose and cumbersome terminology now in use.

The fact that the secretion of placental gonadotropins is initiated at the approximate time of implantation of the blastocyst suggests the probability that they are instrumental in furthering luteal function. In the rat this is apparently the principal endocrine function of the placenta. That gestation in the rat cannot continue in the absence of the ovaries seems to imply that the placenta does not play an important part in the secretion of estrogen and progesterone. The situation in the mare and in primates differs from that described for the rat in that the placenta secretes estrogen and progesterone in addition to a gonadotropin. Thus in the mare, monkey, and human being, the placenta has assumed endocrine control of gestation so completely that pregnancy can proceed normally in the absence of the ovaries after a certain stage of pregnancy has been reached. The importance of these observations as contributions to our knowledge of the evolution of viviparity must remain an open question until such studies have been extended to other mammalian groups. However,



the available facts seem to imply that the elaboration of a gonadotropin by the fetal chorion was the initial adaptation which made it possible to extend the period of gestation beyond the limits of the estrous cycle, while secretion of estrogen and progesterone represents a further placental specialization allowing a still longer gestation period.

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THE DEPARTMENT OF BIOLOGY AND THE  
DEPARTMENTS OF MEDICINE AND PHARMACOLOGY  
HARVARD UNIVERSITY, CAMBRIDGE, MASSACHUSETTS



## PHYSIOLOGICAL PSYCHOLOGY

BY CURT P. RICHTER

*Psychobiological Laboratory, Phipps Psychiatric Clinic,  
Johns Hopkins Hospital, Baltimore, Maryland*

During the past few years the field of physiological psychology has undergone a great expansion, chiefly in the direction of psychiatry, medicine, and nutrition. The number of papers published each year in this and the adjoining fields has become so great that the literature has gone beyond the compass of any individual reviewer. Under this heading we should have to include the reports of the important advances that have been made in electroencephalography (1 to 5); in nutrition (6 to 13); in treatment of mental disturbances by frontal lobectomy (14 to 18), by electrical shock (19 to 27), and by hormones (28 to 36); in the field of animal behavior by the production of fits in rats by sounds of high frequency (37 to 40); and in studies on pain (41 to 47). On account of the great number of papers and the multiplicity of interests which they include, the present reviewer has decided to limit his review to the material with which he has had some first hand experience and which may be included under the general heading of "total self-regulatory functions" which, as will be shown, constitutes a part of Claude Bernard's concept of the maintenance of a constant internal environment (48).

Bernard showed that, in mammals, life depends upon the maintenance of a number of different functions at fairly fixed levels. These functions were concerned to a large extent with the fluid matrix of the body, the salt and sugar content, etc. He described numerous mechanisms which serve the purpose of maintaining these functions at their fixed levels. Cannon (49), on the basis of the results of his own experiments, arrived at much the same conclusions and greatly elaborated Bernard's concept. The mechanisms with which Bernard and Cannon were concerned were limited almost exclusively to physiological functions—that is, functions of separate organs or combinations of organs. Thus, when external cold threatens to lower body temperature, heat is produced by shivering and by burning of fat and is conserved through the reduction of activity of the sweat glands and constriction of the peripheral blood vessels. In extension of this concept, it has now been found in a variety of experiments that the maintenance of a constant internal environment is achieved not only by these part



or physiological responses but also by behavior or total organism responses (50, 51). It is well known that the sodium content of the blood is maintained at a fairly constant level by the secretions from the cortex of the adrenal gland. After removal of the adrenal gland—that is, after removal of the physiological regulator—sodium passes out in the urine in excessively large amounts, thus producing profound changes in the body chemistry which result in grave symptoms and finally death. However, when given access to sodium chloride, adrenalectomized animals ingest sufficiently large amounts to keep themselves alive and free from symptoms of insufficiency. The ability of the rat to maintain a normal sodium blood level and to survive after complete removal of the physiological regulator is thus an example of the existence of behavior or total organism regulation. Many other similar instances have been cited. Rats, which through thyroidectomy or hypophysectomy have lost their physiological means of maintaining a normal body temperature, will make an effort to achieve this end by building large nests to conserve their heat. In this same way rats, which have lost their physiological means of maintaining a constant water balance through removal of the posterior lobe of the pituitary, will compensate for this loss by drinking large amounts of water.

The present review, then, will deal with papers published during the past year (*a*) on further instances of self-regulatory activities having to do almost exclusively with nutritive functions in animals and human beings, (*b*) on the sensory and neurological mechanisms involved in total organism regulation, (*c*) on instances in which organisms no longer make an effort to maintain life—that is, when the self-regulatory functions have broken down and faulty adjustments are made which result in death or serious injury, and (*d*) on experimental and clinical efforts to reestablish the self-regulatory urge or to correct faulty regulation.

#### FURTHER OBSERVATIONS ON SELF-REGULATION

During the past year further observations on self-regulatory functions have been limited largely to studies of the special dietary requirements induced by various endocrine disturbances. Thus, after removal of the pancreas it is known that rats kept on a stock diet show a greatly increased appetite and thirst. These changes in behavior can be interpreted as efforts made by the animal to maintain a constant internal environment. The animals are presumably unable to use carbohydrate and, hence, must take larger amounts



of food to satisfy their caloric needs. The forced ingestion of carbohydrate, which usually constitutes a high percentage of a stock diet, increases the blood sugar; in order to excrete at least a part of the excess, the rats drink large amounts of water. When given free access to fat, carbohydrate, protein, and mineral solutions in separate containers, diabetic rats chose large amounts of fat, almost refused carbohydrate, and showed a doubtfully increased appetite for protein and for yeast. By virtue of their selections, the experimental animals reduced their total caloric intake to normal levels, corrected their polydipsia and polyuria, and lost their hyperglycemia, definitely indicating that they could use fat but not carbohydrate (52). It is interesting that none of the diabetic rats have been found to manifest a craving for salt, which might have been expected from the previous reports of McQuarrie, Thompson & Anderson (53) that two diabetic children ingested large amounts of salt, and further that administration of salt benefited diabetic patients. It is possible that their two diabetic patients with a marked salt craving suffered from definite damage to the adrenal cortex.

Several further instances of self-regulation in human beings were reported. A boy three and one half years old, who for over two years had kept himself alive by eating enormous amounts of salt, was admitted to the hospital and unwittingly restricted to a normal diet containing the usual amount of salt. As a result, he died in seven days. At necropsy it was found that a tumorous growth in his adrenals had completely obliterated all cortical tissue (54). In another instance a thirty-four-year-old patient with Addison's disease was found to have a marked craving for salt. He often filled his glass of tomato juice half full of salt so that for him the juice became scarcely more than a vehicle for the salt. He covered his steak with an even layer of salt about one eighth inch thick. He used salt on grapefruit, oranges, and even on lemons (51). Other patients with Addison's disease reported increased appetite for foods with a high salt content—pickles, ham, soups, etc. For the reason that salt may often be obtained by these patients as a part of other foods rather than by itself, it is necessary for a full dietary history to be obtained before the presence of a salt craving can be determined.

Further observations were also made on the dietary selections of rats given access to an assortment of substances which lacked various components of the vitamin-B complex. It had previously been shown that when deprived of all components of the vitamin-B



complex rats developed a fat craving, a partial aversion to carbohydrate, and a total aversion to protein. Given access to thiamin chloride, they lost their carbohydrate aversion but still completely refused protein. Progressively as the solutions of the other crystalline vitamin-B components were added for choice, they ate more protein, less fat, and more carbohydrate, grew better, and showed better maintenance of their endocrine glands. Given access to thiamin, riboflavin, nicotinic acid, and B<sub>6</sub>, some of the animals showed almost normal growth and maintenance of their endocrine glands. Their appetite for carbohydrate and fat closely approximated the normal levels, but their protein appetite still fell definitely below the normal level. The assortment of substances offered for choice must still have lacked important dietary essentials, such as, for instance, pantothenic acid, biotin, or choline chloride, all of which are present in yeast (55).

Bodansky & Duff (56) reported that parathyroidectomized rats manifested an increased appetite for foods with a high calcium content and a decreased appetite for foods with a high phosphorus content.

Carlson (57) observed that gray squirrels during pregnancy and lactation ate bones apparently to satisfy a phosphorus and calcium need. Woodbury (58) observed that discarded antlers often show signs of having been gnawed at and partly eaten by rodents. He suggests that rodents may be responsible for rapid disappearance of antlers from the field. Coventry (59) during an entire summer watched a red squirrel gnaw away at the projecting parts of an old moose skull. Since the bone eating continued beyond the breeding season, it appeared that it must have fulfilled more general needs.

Abbott (60) reported that, in the South, pregnant negro women have a great craving for what is known as stump dirt,

... the dirt found where a large tree blows over and brings up a clay subsoil. During pregnancy there is apparently a feeling of need of a certain element. These women go long distances and bring back buckets of this clay which they eat to supply the developing fetus. Our examination of pregnant women has shown some with hemoglobin levels between 35 and 40 per cent. So the need for iron in these particular cases is very great.

However, since pregnant and lactating rats manifest such marked craving for calcium and phosphorus (61), it is not unlikely that these women may have been making an effort also to correct a deficiency of these minerals.



## MECHANISMS INVOLVED IN SELF-REGULATION

The evidence at hand indicates that the self-regulatory dietary behavior of rats depends largely on taste and not on experience. After section of the taste nerves, adrenalectomized rats failed to differentiate between sodium chloride solution and water and, as a result, died almost as quickly as adrenalectomized rats without access to salt (62). Further, it was found that rats accepted or refused solutions of electrolytes according to their dietary value in extraordinarily low concentrations which could not possibly have had any physiological effect. Adrenalectomized rats preferred a sodium chloride solution to water in concentrations of one part of salt to 33,000 parts of water, while normal rats show no preference until a concentration of one part of salt to 2000 parts of water is reached (63). This must indicate that the operated animals have a sodium deficit throughout the body, including the taste buds of the tongue. When, under these circumstances, sodium chloride solution comes into contact with the taste buds, the concentration gradient must be such that its taste can be perceived. This appetite may be a manifestation of a chemotropic response as was suggested by the earlier observations of Turro (64) and Mursell (65).

These observations have stimulated a new interest in the various gustatory mechanisms involved in dietary response. It becomes of special interest to determine the roles played in dietary selections by the constitution of the saliva and by the chemical and mechanical construction of the various taste papillae—fungiform, foliate, and circumvallate—and of the taste buds. It must be determined whether the structure of the taste buds and papillae change with age, whether the changes are correlated with functional changes in taste, whether individual differences in taste ability depend on structural differences in taste papillae and taste buds, and finally whether these functional and structural differences are inherited. On the structural study of the tongue, several workers have carried on investigations similar to those reported by Arey and his collaborators (66) on changes in number of papillae with relation to age. Mochizuki studied the number of foliate papillae in the tongue of Japanese and also the number of taste buds with relation to age and sex (67, 68); and Ogawa pointed to probable hereditary factors influencing the pattern of the circumvallate papillae (69). Elliott and his students have recently made counts of taste buds on the fungiform and circumvallate papillae in kittens and pups (70, 71, 72).



Physiological studies have also been made on the taste papillae. The studies of Pfaffman (73) are most noteworthy. His observations on the electrical impulses produced in the chorda tympani and glossopharyngeal nerves by stimulation of the taste buds on different parts of the cat's tongue with various substances open up an entirely new approach to this problem. This method makes possible the study of gustatory sensitivity in animals which hitherto was confined only to human beings. By microdissection of the taste nerves of cats he was able to isolate three types of fibers: (a) those which respond to acid only, (b) those which respond to both acid and sodium chloride, and (c) those which respond to both acid and quinine. No fibers responding to sugar were found. Using this technique, the apex and anterior lateral margins of the cat's tongue were found to be most sensitive to salt, the base and posterior lateral margins to quinine, and all regions except the mid-dorsal were sensitive to acid.

Pfaffmann (73) concluded from his results that different types of sensory endings, each of which responds only to certain chemical solutions, constitute the sense of taste. He believes that in human beings stimulation of one set of fibers will produce a salt taste. When discharges in the same fibers are combined with activity in all the remaining gustatory fibers, a sour taste is produced. "In such a system sensory quality does not depend simply on the 'all or nothing' activation of some particular fiber group alone, but on the pattern of the other fibers active."

*Peripheral nerve mechanisms.*—The dependence of the dietary selections on taste is clearly demonstrated by results of experiments on the effects produced by section of taste nerves and the ability of adrenalectomized rats to compensate for the disturbance of their sodium metabolism. It was found that, while removal of the olfactory bulbs had no effect on this ability, combined section of the lingual nerves, including the chorda tympani and the glossopharyngeal nerve, abolished this ability. The rats no longer ingested more salt and, as a consequence, died within the usual time, ten to twenty days. Of interest from the neurological point of view was the observation that combined section of the chorda tympani and the glossopharyngeal nerve without section of the lingual nerves did not fully abolish this ability; the rats still increased their sodium chloride intake and survived (62). Preliminary results indicate that, in accordance with Pfaffmann's results, the



ability to make beneficial selections of sugar solution may depend on other nerves.

*Cortical taste mechanisms.*—Two papers by Börnstein (74, 75) contain a review of our knowledge regarding thalamic and cortical gustatory mechanisms and a report of clinical observations made on patients with brain injury. From his reading of the literature and from clinical observations he concluded that the belief in a close relationship between taste and smell mechanisms which has long been held by most writers is not substantiated by the facts. His observations point to a close relationship between touch and taste. Thus, he states (74):

From considerations such as the above, it was believed that the functional relations which taste bears to tactile function predicate a convergence in the cortex of these two kinds of sensation rather than of the gustatory and olfactory pathways. The anatomical similarity of the gustatory and tactile system at the level of the sense organs, of the peripheral nerves, and of the primary synapse is, of course, an even stronger basis for assuming a retention of their similarity at the level of the cortex in the form of a contiguous cortical representation in the parietal operculum.

It may be remarked at this point that the assumption of a close relationship between taste and smell may have given rise to much confusion in this field of research. Many workers still hold that taste is largely a matter of smell. In agreement with reports of Harlow (76), the results of self-selection studies have shown thus far that complete removal of olfactory bulbs did not in any way alter the dietary selections of rats. In the same way taste threshold studies made on a number of different substances in human beings were much the same regardless of whether or not the olfactory functions were largely eliminated by bad colds. Smell would thus appear to play much the same sort of auxiliary role as vision in the selection of foods, the final ingestion of the food depending on taste. Experimental studies made by Ruch, Blum & Brobeck (77) on taste disturbance produced by thalamic lesions in monkeys bring further evidence in support of Börnstein's "opercular theory." These experiments yielded a number of interesting and important results. A paper by Blum (78) contains a detailed account of the experimental procedure and also a valuable bibliography of papers on the neurology of taste. Blum concluded from observations made with objective taste tests on three monkeys with thalamic lesions that "afferent fibers conducting taste impulses reach the posterior ventral portion of the thalamus, and probably relay in the arcuate nucleus," and further "that taste and somatic sensa-



tion from the tongue are contiguously represented in both the thalamus and cortex is suggested by the correlation of our findings with other physiological and anatomical data."

*Taste ability.*—Of great interest for the study of self-regulatory dietary selections is the determination of the inheritance of taste ability for various purified substances. The pioneer work of Blakeslee (79) and Snyder (80), who found that a small percentage of human beings is not able to taste the bitter phenylthiocarbamide and that this inability is inherited as a Mendelian recessive has been extended by further observations during the past year by Matson (81), Sewall (82), and Hartmann (83).

The extent to which this inability to taste phenylthiocarbamide extends to other substances has not yet been clearly established. In our taste threshold studies we have found individuals who could not recognize a 10 per cent sucrose solution, while average normals recognized it in concentrations of 0.41 per cent (84). In preliminary experiments it was found that some individuals are unable to recognize alcohol at any concentration and that about 7 per cent will drink solutions as high as 50 per cent without finding them unpleasant or distasteful. Most normal persons reach this point with concentrations from 0.5 to 10 per cent.

Young (85) has used a quite different approach, calculated to determine the relative appetite of the rat for two substances (for example, sugar and wheat) offered in addition to a basic diet rather than absolute appetitive demand for any one substance. The technique used is quite different in that the observations concern an immediate choice made within a few minutes between two containers when the rat is first released from a starting box. Further, the foods tested often answer quite different nutritive needs of the body (that is, sugar and wheat), so that it is at present difficult to correlate his results and conclusions with those reached by the self-selection technique.

In order to determine how much of a substance has to be present in a food or solution to be tasted by rats, taste threshold determinations were made for a variety of different substances by determining the lowest concentration at which the animals show a consistent preference, either for the solution or for water.

Thresholds were determined for five common sugars—maltose, dextrose, sucrose, galactose, and lactose. The rats showed the lowest threshold for maltose, 0.06 per cent, and the highest for lactose, approximately 2.20 per cent (86).



After threshold determinations had been made on a number of different substances, it became evident that a close relationship exists between the preferences shown by rats for different purified substances and the nutritional value of these substances. Thus far it has been found that all substances which in some concentrations the rats preferred to water had a definite nutritional value—maltose, dextrose, sucrose, galactose, sodium chloride, sodium phosphate, potassium chloride, etc.—while substances which were not preferred in any concentration had no nutritional value or were actually poisonous, such as, for instance, mercuric chloride, arsenic trioxide, etc. (87).

Rats preferred alcohol in concentrations of 1 to 6 per cent and in higher concentrations preferred the water to the alcohol. Alcohol was thus placed in the group of substances which have a nutritional value. The value of alcohol as a food was further demonstrated in experiments in which all of the drinking water made available to the rats in the form of 8, 16, or 24 per cent solutions of alcohol respectively. These rats reduced their food intake directly in proportion to the caloric value of the intake of alcohol, the total caloric intake remaining the same. The fact that these rats maintained their weight and remained in good physical condition was taken as evidence that alcohol had successfully replaced the decrease in food intake (87).

It was found that when the concentration of a solution was successively increased beyond the threshold the intake increased to a peak and then decreased to a low level again. The concentration at the peak intake was called the maximum preference concentration. For four of the sugars the maximum preference concentrations were: maltose, 10.0 per cent; sucrose, 8.0 per cent; dextrose, 11.0 per cent; and galactose, 9.0 per cent. The rats did not at any time prefer lactose to water. For the dextrose and maltose these concentrations coincided with the highest concentrations which can be absorbed from the stomach, according to Groen (88).

Tests made on human beings, using a similar technique, showed that rats and human beings have very nearly the same taste threshold for sucrose and for the bitter tasting phenylthiocarbamide (89). It had previously been shown that they have the same threshold for sodium chloride. It is likely, since the taste sensitivity seems to depend on blood concentrations, that thresholds will be very nearly the same in the two species for any substances occurring in equal concentrations in their blood streams.



INSTANCES OF A BREAKDOWN OF THE SELF-REGULATORY  
BEHAVIOR MECHANISMS

From the foregoing discussion it is conceivable that the self-regulatory dietary selections may break down at several points and thus end in the death of the individual. An individual who is unable to taste phenylthiocarbamide could, if exposed to this substance unknowingly, take sufficiently large amounts to end in his destruction, since phenylthiocarbamide has been shown to have a very highly toxic action. In the same way faulty dietary choice for other substances may rise either from an inherited inability to taste particular substances or loss of the ability to taste, due to neurological disturbances, the ingestion of large amounts of highly concentrated alcohol, or other causes. Individuals who do not get the warning sensation from alcohol in small concentrations may take injuriously strong and large amounts of this stimulant (87).

The numerous cases of anorexia nervosa seen in medical and psychiatric clinics may, at least in part, be instances of breakdown of self-regulatory behavior (90, 91, 92, 93). Many of these patients, if not forced to eat, will take no food at all and, as a consequence, die within a short time. The greatly reduced food intake may, however, even in this case, be an instance of self-regulatory behavior. For example, we know that rats deprived of their pituitary glands show a greatly reduced food intake, presumably to compensate for their poor absorption and the difficulties of metabolism resulting from decreased thyroid secretion. On this reduced food intake they may live for many months (94). Some of the anorexia patients may also be in states of profound vitamin-B deficiency from which they can be rescued only by treatment with large amounts of the entire vitamin-B complex.

Brain injury or destruction may also cause faulty regulation. Rats deprived of the tips of the frontal poles of the brain may eat almost incessantly, as was demonstrated by Richter & Hawkes (95) and by Beach (96); or rats or monkeys with lesions of the thalamus may eat until they become very obese, as was reported by Hetherington (97), Hetherington & Ranson (98), and Ruch, Brobeck & Blum (99). It is very likely that monkeys with complete agusia produced by lesions of the arcuate nucleus, such as were made by Ruch, Brobeck & Blum, would if exposed to non-nutritive or poisonous foods quickly exterminate themselves. It is only with the greatest difficulty and deception that normal monkeys can be made to take drugs or other harmful substances.



Monkeys and apes will detect even the most minute pieces of sedative pills hidden away inside such foods as bananas, oat meal, and applesauce and will refuse to eat more of the food.

#### EFFORTS TO RE-ESTABLISH SELF-REGULATION

Experimental data on this phase of self-regulatory studies are still lacking. Clinically we have some data which may belong under this heading. Freeman & Watts (14, 16) have reported that psychotic individuals, who for long periods of time made no effort to feed themselves or to take care of themselves in other ways, started to eat spontaneously again after frontal lobectomy and to show other self-regulatory responses. According to this point of view the frontal lobes may, like the appendix, be the source of trouble and equally unnecessary. Whether or not this operation rests on a sound theoretical or practical basis must depend on the results of further investigation. Electrical shock treatment, much used in psychiatric clinics, has been reported to have similar effects in some cases. In this treatment the alternating current is passed through the head directly between the frontal poles of the brain. It may be that these effects are achieved through a temporary or permanent paralysis or destruction of the frontal poles.

The striking effects produced by treatment with thiamin chloride, nicotinic acid, and B<sub>6</sub> on individuals who seemed to have lost all of their self-regulatory responses may also be grouped under this head. Spies *et al.* (10) have reported that patients who had shown little or no appetite began to eat and show normal responses almost at once after treatment with nicotinic acid or B<sub>6</sub>.

#### SUMMARY

The results obtained thus far from self-regulatory studies indicate the following: (a) The effort to maintain a constant internal environment constitutes a fundamental behavior drive. (b) The self-selection technique gives us a method of determining chemical and metabolic needs which might be determined by biochemical methods only after prolonged experimentation. (Thus, for instance, with this technique we might have determined many years ago, long before the development of modern biochemical methods, that the adrenal glands are concerned with the regulation of sodium metabolism. It would only have been necessary to offer rats a choice of a number of different electrolytes and foods. The immediate selection of electrolytes containing sodium would have shown



that removal of the adrenals had disturbed the sodium metabolism. In the same way this method could have demonstrated that the parathyroid glands are concerned with the regulation of calcium metabolism, the pancreas with the regulation of carbohydrate metabolism, etc.). (c) Instances of markedly unusual behavior observed clinically may be considered as manifestations of efforts by the individual to maintain a constant internal environment. (The polydipsia of patients with diabetes insipidus would thus be regarded as an effort to compensate for the increased water loss due to the absence of the antidiuretic hormone from the posterior lobe and not simply to the presence of a lesion in a hypothetical thirst center in the brain.)

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PSYCHOBIOLOGICAL LABORATORY, PHIPPS PSYCHIATRIC CLINIC  
JOHNS HOPKINS HOSPITAL  
BALTIMORE, MARYLAND



## APPLIED PHYSIOLOGY<sup>1</sup>

By A. R. BEHNKE, *Lieutenant Commander (MC), U. S. N.*  
*Laboratory, Experimental Diving Unit, Navy Yard, Washington, D. C.*

AND

C. S. STEPHENSON, *Captain (MC), U. S. N.*  
*In Charge, Division of Preventive Medicine, Bureau of Medicine  
and Surgery, Navy Department, Washington, D. C.*

A prime need in the military service is the application of physiologic knowledge to field practice. We have only to turn to developments in Europe to realize the value of contributions made by physiologists and biochemists in enabling men to cope with adverse environments.

In Germany, for example, for a period of at least five years as many as twenty government-supported laboratories (1) were equipped with low pressure chambers devoted to research in military flying. By contrast, during the same period the United States had only one physiologic laboratory engaged in aeronautical investigation.

The seriousness of the error in not continuing aviation research following the notable contributions of American physiologists (2) during the last World War is now apparent. Steps to improve conditions have been taken by the National Research Council which is coordinating investigative endeavor in the universities (3) and in both branches of the Service to the end that military field practice will reflect the latest findings of the physiologic laboratory.

In that phase of Service activity dealing with submarines and deep sea diving, however, systematic, continuous investigation has been carried out over a period of years.

That these endeavors (4) were to culminate in successful rescue and salvage efforts incident to a submarine disaster is but a consequence of careful preparation and ground work in physiology as applied to naval operations.

<sup>1</sup> The present review deals with physiological applications in military practice. The material in this article should be construed only as the personal opinion of the writers and not as representing the opinion of the Navy Department officially.



## PART I. AVIATION

## SURVEYS OF CURRENT PROBLEMS

Recent papers contributed by Fulton (1), Whittingham (5), Ryan & Hall (6), Ceres (7), Poppen (8), Grant (9), Boothby, Lovelace & Benson (10), and Behnke & Willmon (11), reflect the newer problems in contrast with those of the last World War, arising especially in connection with high altitude flying and the power dive and covering such topics as aeroembolism, adequacy of oxygen supply, protection against low temperatures, and accelerative changes leading to the "blackout."

Long-continued flights, moreover, have led to an appreciation of the time factor in the development of symptoms of altitude anoxia so that inhalation of oxygen is recommended at altitudes as low as 8000 feet.

The perennial difficulty of determining the psychological and psychomotor qualifications for flying may resolve itself when the results of current tests employing objective methods become known.

Air sickness (1) arising from sudden acceleration in any direction in space may be mentioned as a grave problem which is the least understood of all the forms of physiologic breakdown.

A distinct advance in the training and indoctrination of personnel as well as testing personnel for ability to accommodate to pressure change and to resist the symptoms of aeroembolism, lies in the employment of numerous low pressure chambers now in the process of installation or operation at air base centers.

## PRESSURE PHENOMENA: PRIMARY EFFECTS

Behnke (12) makes the distinction between primary pressure phenomena and the reactions arising from alterations in gaseous pressure in the lungs and in the body tissues.

Pressure *per se* in the range of one seventh of an atmosphere, equivalent to 45,000 feet altitude, to sixteen atmospheres, equivalent to a diving depth of 500 feet, is apparently without physiologic effect provided that the orifices leading to the air cells and spaces of the ear and of the paranasal sinuses are patent. Hydrostatic pressure, however, of the order of one hundred atmospheres or greater induces striking alterations in morphology and function of protoplasm as demonstrated by Cattell (13).



*Aero-otitis media.*—Obstruction of the nasopharyngeal orifice of the auditory tube brought about usually by acute or chronic infection of the upper part of the respiratory tract gives rise to difference in pressure in the air spaces of the ear and the surrounding tissues, when barometric pressure is altered in altitude flying or aqueous diving. Essentially a cupping action is produced by the difference in pressure giving rise to congestion, edema, and hemorrhage (12). A new mechanism inducing trauma is brought about by the absorption of oxygen in the aural spaces following inhalation of oxygen during high altitude flight. This leads to a cupping action and the typical changes in the ear already described when voluntary opening of the auditory tubes is suppressed during sleep (11).

The effect of this pressure trauma on the aural tissues has been designated by Armstrong & Heim (14) as *aero-otitis media*. The entity is identical with the traumatic injury to the ear appearing in caisson workers and divers described by Heller, Mager & von Schrötter in 1900 (15).

The incidence of partial blockage of one or both auditory tubes preventing rapid equalization of pressure at the rate of two atmospheres per minute in aural spaces may be as high as 10 to 15 per cent in submarine personnel (16). For aviators a similar incidence holds for a corresponding pressure change of one fourth to one half atmosphere, or one half to one atmosphere, i.e., 18,000 feet to ground level, occurring during a period of a minute (11).

In civil aviation, however, Tuttle (17) reports that only one passenger out of thirteen hundred had ear trouble. This low incidence of obstructive pressure otitis may be due to the stipulation that the maximum rate of descent for civilian passengers must not exceed 300 feet per minute.

*Effect on hearing.*—A great deal of confusion exists with regard to the effect of pressure trauma on auditory acuity. Following acute trauma the audiogram reflects diminished perception of sound over the whole frequency range. As the pathologic disturbance undergoes resolution, however, hearing returns to the initial level of acuity (18). There are no proved cases of deafness arising from injury incident to pressure trauma in deep sea diving or caisson work. This fact stands in contrast to the permanent damage to the cochlea with diminished reception of certain frequencies due to excessive noise.



Campbell & Hargreaves (19) describe impairment in hearing occurring in the lower frequency range following simulated altitude descent at the rate of 1000 feet per minute. These authors consider that faulty ventilation of the middle ear is one of the causes of deafness in aviators.

Examination by Pastore (20) of 88 pilots showed that 42 had normal hearing, 16 suffered impairment attributed to nerve deafness, while 22 showed a hearing loss designated as conductive impairment. The zone of greatest loss in hearing is the frequency level of 4096 double vibrations, presumably corresponding to a cochlear area exposed in position and possibly having a deficient blood supply (19).

The classification, however, of auditory impairment on the basis of either perception or conduction deafness depending upon whether the high or low frequency range is primarily affected, requires reexamination in view of Crowe's finding (21) that occlusion of the pharyngeal orifice of the auditory tube may lead to impairment in reception of both high and low tones.

Audiograms recorded on deep sea divers and musicians showed consistent loss of hearing in the frequency range of 4096 vibrations (11). The conclusion drawn from these results was that occasional traumatic injury elicited by pressure did not permanently injure the hearing mechanism.

Noise and possible vibrations outside of the hearing range have been associated with loss in auditory acuity both in aviation and industry (22, 23, 24).

The investigations of Campbell & Hargreaves (19), Pastore (20), Dickson, Ewing & Littler (24) confirm the association of excessive noise with loss in hearing.

*Measures to relieve obstruction in tubal orifices.*—The inhalation of a mixture of helium and oxygen has been proposed by Lovelace, Mayo & Boothby (25), by Crosson, Jones & Sayers (26), and by Requarth (27) as an aid to equalization of ambient pressure in the spaces of the middle ear on the basis that helium diffuses more rapidly than nitrogen through restricted tubal orifices.

Behnke & Willmon (28) observed, however, that divers had difficulty equalizing pressure when suffering from "colds" irrespective of whether air or helium-oxygen mixtures were breathed. It is likely that if some benefit accrues from the use of helium, it is obtained by transport of gas in the blood stream. Hall (29),



moreover, was unable to ascertain any real advantage in the use of helium-oxygen combination for the alleviation of tubal obstruction.

A maneuver consisting of forced inspiration following forced expiration with the nostrils and mouth held closed has been described by Lamport (30) as a remedial measure tending to overcome tympanic vacuum.

Remedial measures or maneuvers are at best only palliative and the attainment and maintenance of patency in the obstructed tubal orifice are still to be achieved.

*Gaseous distension of the stomach and intestines.*—One of the most distressing responses accompanying rapid diminution of ambient pressure corresponding to altitudes above 30,000 feet follows the expansion of gas present in the stomach and the large bowel (11). Preventive measures are aimed primarily at limitations of air swallowing by abstinence from eating or gum chewing prior to flight.

#### PRESSURE PHENOMENA: DISTURBANCES OF GASEOUS EQUILIBRIA INCIDENT TO PRESSURE FLUCTUATIONS

The more serious manifestations of a rapid change in pressure incident to high altitude flight arises from altered gas tensions in the lungs and body tissues.

*Anoxia.*—The need for oxygen at altitudes of 10,000 feet and higher is generally recognized in the military service. The current problem is to provide adequate equipment for oxygen inhalation and to familiarize flying candidates with the symptoms of anoxia. While veteran aviators are familiar with the increase in reaction time, visual dimness, change in mood, drowsiness, lassitude, headache, and fatigue, it seems desirable to have some simple instrument available in actual flight to indicate objective impairment.

That a great variation even in highly selected men exists in regard to the oxygen "ceiling" (10) is not surprising. Of importance is the question of the altitude at which compensatory changes are observed as a result of the fall in pulmonary oxygen pressure.

Fulton (1) speaks of the physical inertia that may accompany altitude flight above 5,000 feet. White (31) in electrocardiographic studies obtained on forty-five normal subjects detected a quickened pulse rate and evidence of diminished voltage in the T waves



above 5,000 feet. Benson (32) in a series of similar observations reported that cardiac rate was increased beginning at altitudes of about 8,000 feet. Up to 20,000 feet, however, there appeared only a slight and inconstant depression of the T wave and a decrease in amplitude of the QRS complex. No change in the electrocardiogram was recorded when subjects breathed pure oxygen at an altitude of 30,000 feet.

White (33) stresses the need for careful examinations in older pilots with reference to the possible occurrence of coronary occlusion. He cites the death immediately following a flight of a 27-year-old pilot from coronary heart disease, and he suggests that oxygen deficiency may hasten the development of degenerative vascular disease.

*Alveolar carbon dioxide, and blood pH.*—Hinshaw & Boothby (34) admonish against the practice of hyperventilation at high altitudes and enumerate the symptoms of dizziness, faintness, tingling, and numbness of the fingers associated with a rapid fall in alveolar carbon dioxide pressure.

Fulton (35) has clarified the alterations in blood pH arising from the disturbed carbon dioxide tension during ascents to high altitudes.

Inhalation of oxygen in place of air does not appreciably affect the usual carbon dioxide pressures (11).

*Aeroembolism.*—Fulton (1) refers to Robert Boyle as "the father of aviation medicine," since Boyle in addition to making fundamental deductions regarding pressure phenomena, first subjected animals to rapid decompression and described the phenomenon designated as "aeroembolism" by Armstrong (36).

The results of a considerable amount of recent work on aeroembolism are not available for publication. However, the knowledge derived from the field of deep sea diving and caisson work is applicable to the problem.

Since the classic experiments of Paul Bert, decompression symptoms have been attributed to gas bubbles either present as emboli, or in tissues, joint spaces, and cerebrospinal fluid.

Behnke *et al.* (37) have observed bubbles only in the blood vessels of dogs rapidly decompressed from high pressure atmospheres. It is believed that "bends" arise from nitrogen bubble formation in the vascular network of the medulla and cortex of bone (12).



That the symptoms attributable to aeroembolism have the same etiologic basis as compressed air illness was apparent in divers rapidly decompressed to altitudes equivalent to 35,000 feet. The rapid amelioration of symptoms during recompression, i.e., altitude descent, is in accord with an etiologic picture of gas embolism rather than with tissue injury brought about by extravascular bubble evolution.

Agglutination of red blood cells is believed by Swindle (38) to be a more important factor than air embolism in the etiology of decompression symptoms.

Hemoconcentration amounting to as much as 30 per cent in dogs, was demonstrated by Behnke, Shaw *et al.* (37) to be characteristic of extensive embolism. It is likely that cell packing and not agglutination is present under these conditions.

The cerebrospinal fluid pressure was found by Armstrong (36) to be increased at altitudes above 18,000 feet. Walsh & Boothby (41) corroborated this finding and demonstrated bubbles in cerebrospinal fluid of man at a simulated altitude of 10,000 feet. Spinal fluid pressure rose from 8 to 11 cm. in ascent to 28,000 feet, Behnke & Willmon (11) on the basis of lumbar and cisternal punctures in goats concluded that the small increase in cerebrospinal fluid pressure observed at 40,000 feet was not a factor in producing decompression symptoms. Forcible inflation of the lungs, for example, induced a rise in pressure of the same order as that observed in altitude ascent. Since the introduction of a needle may initiate bubble formation in supersaturated fluid a roentgenologic demonstration is a more valid criterion of the presence of free gas in the ventricles.

Intraocular pressure in rabbits subjected to altitude ascent to 40,000 feet, at the rate of 1,000 to 3,000 feet per minute, remained unchanged (42).

*Fatigue as a complication of aeroembolism.*—One of the most interesting symptoms rather frequently experienced by divers as a result of too rapid decompression is fatigue (43). Fatigue likewise was observed (11) following exposure to simulated high altitudes. Under the circumstances of its occurrence it is regarded as a manifestation of the presence of aeroembolism.

*Treatment and prevention.*—Immediate descent to lower altitude clears up the symptoms of aeroembolism (1, 10, 11). No complications are observed except occasional fatigue, and residual



soreness in the chest following what appears to be extensive pulmonary embolism referred to by compressed air workers as the "chokes."

The elimination of the dissolved nitrogen in tissues by oxygen inhalation prior to altitude ascent serves to prevent aeroembolism (10, 11).

The time required for complete nitrogen removal extends over a period of nine to twelve hours (39). Moderate exercise augments the elimination of nitrogen during the first half hour (10, 39). It is not certain, however, that exercise appreciably affects the removal of the nitrogen in bones, the source of bubble formation leading to "bends."

#### PHYSIOLOGIC EFFECTS OF RAPID CHANGES IN MOTION

*The power dive.*—In vertical power dives aeroplanes may attain velocities of 600 miles per hour. During the turnout from the vertical fall all movable fluids tend to be carried from the head to the feet by the action of centrifugal force (1). The pilot may experience a temporary loss of vision for a period of several seconds to minutes, followed by temporary loss of consciousness known as the "blackout."

Poppen about nine years ago in an unpublished report demonstrated the changes in blood pressure occurring in anesthetized dogs subjected to actual power dives. These findings have been corroborated by Armstrong (36).

Measures to prevent the "blackout" are directed at keeping the blood cephalad. The unaided pilot cannot successfully come out of a dive when his acceleration is more than 5g, i.e., five times the normal acceleration of gravity (1). Abdominal supports will increase the range of acceleration about 2g (8). The assumption of the crouching position by German pilots is most effective since it serves to lessen the distance through which the force of gravity acts to deprive the brain of fluid.

*Air sickness.*—This term refers to the physiologic breakdown which accompanies sudden acceleration in any direction of space with consequent stimulation of the vestibular system (1). The same fundamental derangement appears to operate in seasickness.

There is no single medical problem of greater importance in the Navy and there is, on the other hand, no field in physiology so barren with respect to the application of results as is the study of accelerative disturbances of unaccustomed motion.



Repeated training in a Bárány chair, and administration of atropine and sedatives may be of aid, but no regime has been worked out that serves as a certain preventive. An abdominal support is said to offer some protection (40).

#### SELECTION OF PERSONNEL

The qualifications for aviation training are the most rigid in the military service. Mashburn (44) states that of the several thousand college men examined annually for air corps training, 80 per cent failed to pass the physical examination. Of the remaining 20 per cent less than one half demonstrate adequate proficiency for flying.

With reference to experienced civil air line pilots Tuttle (45) observed that they had many of the characteristics of the athlete. Pulse rates tended to be slow, blood pressure low, and there was an absence of signs of vasomotor instability. The pilots were stable, dependable, and well poised. Noteworthy was the absence of dramatic personalities or unusually brilliant persons.

In the physical examination of 679 candidates for flying, Leedham (46) found that 138 or 20.3 per cent were rejected by reason of vasomotor instability which he considered to be a minor degree of neurocirculatory asthenia characterized by a low Schneider index, unstable blood pressure and pulse rate, and a coarse tremor.

Bartlett & Carter (47) stress the value of the routine use of the electrocardiograph and stethograph in the examination of candidates for aviation. In ten cases of heart disease reported the electrocardiogram was essential in the diagnosis of eight disorders.

McFarland, Graybiel, Liljencrantz & Tuttle (48) believe that the tilt table test designed to measure circulatory changes in relation to posture might be of value in estimating susceptibility to the "blackout."

As a test of pilot fitness Ferree & Rand (49) have perfected over a period of years the tachistoscope devised to measure the speed of adjustment of the eyes for change of distance, speed of accommodation, and adaptation. While intermittent reports have appeared with reference to this type of equipment, its employment has not been widespread as a means of determining fatigue either ocular or general. In this connection the ophthalmograph used in the studies of Jones *et al.* (50) showed promise.

*Physiologic-psychologic considerations.*—Although the compre-



hensive physical examination prevents subsequent failures in flight training due to somatic deficiency, the psychological examination, especially evaluation of emotional response, has not been satisfactory.

A potentially useful test, which embodies extensive studies of psychophysiologic effects of reduced oxygen pressure by McFarland (51) and others, consists in subjecting an individual to oxygen deficiency in the low pressure chamber. It is difficult to understand why the sound principle of placing a "load" on the nervous system to estimate psychic reserve is not standard practice. Yet there is no uniform procedure in the military service for the evaluation of an individual's emotional or nervous stability under the stress of anoxemia.

Bigelow (52) considers that as many as 90 per cent of failures to complete courses in military aviation are on a psychologic basis. Of the psychologic aspect of the problem estimation of emotional reactivity by means of the Rorschach test is expected to be the most useful. Subjective tests in the form of questions and answers have been found to be of little value in that a candidate tends to give what he thinks is the answer most favorable for his selection.

Harrower-Erickson (53) is in agreement with Bigelow (52) with respect to the potential value of the Rorschach test which he looks upon as an objective measure of nervous stability. This type of test is now undergoing extensive trials at the Naval Air Base, Pensacola, Florida.

With respect to tests of special flying aptitude involving psychomotor reactions, the Mashburn serial action test employing apparatus simulating rudder and control stick in a small aeroplane, showed a high degree of correlation between the time required to complete the test and ability to fly (48). Another method productive of results which might be expected to correlate even more closely with flying aptitude is the Link trainer (52).

## PART II. PHYSIOLOGIC EFFECTS OF GASES AT HIGH PRESSURES ESPECIALLY IN RELATION TO DEEP DIVING AND THE SUBMARINE SERVICE

In contrast with the cessation of aviation research, the basic studies of DuBois (54) and Brown (55) during the last World War were continued at the Harvard School of Public Health and later



at the Experimental Diving Unit, Navy Yard, Washington, D. C.

The pressure chamber as employed in these studies opens up a new field for physiologic investigation. While naval medical officers have made contributions directed primarily to improvement in field practice, there have appeared facts of general physiologic interest, which for the most part have failed to stimulate research endeavor on the part of investigators in civilian laboratories.

In this connection mention may be made of such phenomena of oxygen poisoning as the convulsive seizure, contraction of visual fields, nausea, and the development of oxygen allergy. The fact that the oxygen in physical solution is adequate for tissue requirements at a pressure of three atmospheres during oxygen inhalation could well serve as a means for additional studies of the function of hemoglobin. Other phenomena worthy of intensive study are the relationship between carbon dioxide and oxygen at high pressures, the narcotic effect of atmospheric nitrogen, the value of helium in preventing this impairment, the diffusion of helium through skin, and the hemoconcentration accompanied by a shock-like state appearing in animals rapidly decompressed from high pressure atmospheres.

#### HIGH OXYGEN PRESSURES AND OXYGEN POISONING

Mention must be made of the paucity of experiments concerning oxygen poisoning. While the literature is replete with contributions concerning the effects of low oxygen pressures, little material is available with reference to the action of increased oxygen pressure on such functions as metabolism, carbon dioxide transport, and the growth of cells.

*Oxygen pressures of 1 atmosphere.*—Paine, Keys & Lynn (56) add further confirmation that the pathologic changes in the lungs of dogs exposed to an atmosphere of pure oxygen for forty-eight hours consist of pulmonary edema and hemorrhagic extravasation. In an atmosphere of 90 per cent oxygen the dogs survived twice as long.

In man, contradictory reports of oxygen tolerance arise perhaps from the failure to consider that healthy men may react differently from patients, and that interruption of oxygen inhalation for short periods of time or a decrease in the percentage breathed fortifies resistance to toxic symptoms. Under certain conditions a concentration of 99 per cent oxygen may be inhaled continuously



for periods as long as seventeen hours (39). On the other hand, symptoms of pulmonary irritation have terminated some tests at the end of seven hours.

Barach (57) reports symptoms of delirium and mental confusion in chronically anoxic patients to whom 50 per cent oxygen mixtures were administered. Adjustment to the higher oxygen concentration took place after several days.

*Oxygen allergy.*—The development of sensitivity to oxygen in the form of dermatitis following repeated exposures of a diver to a pressure of 2.5 atmospheres has been reported by Willmon & Behnke (58). Subsequent exposures at atmospheric pressure had to be terminated after several hours by the onset of nausea, and the appearance of erythema of the face and neck. Administration of histaminase (in the form of Torantil, Winthrop) brought about a remission of symptoms. This finding is of especial interest in view of the work of Campbell (59) pointing to the action of a histamine-like substance in oxygen poisoning.

*Oxygen pressures of 2.5 to 3 atmospheres.*—In diving these pressures usually are not exceeded during oxygen inhalation. No explanation has yet appeared for the remarkable contraction of visual fields, which is reversed when air is substituted for oxygen (60). Nausea, however, is the symptom pathognomonic of the toxic action of oxygen at 2.5 atmospheres pressure (61).

*Oxygen pressures of 4 atmospheres and higher.*—Oxygen inhalation at a pressure of 4 atmospheres, equivalent to a diving dept of 100 feet, may be tolerated for a period of thirty minutes (58). Vasoconstriction manifested by blanching of the facial skin is constantly observed. Nausea, a sensation of cerebral fullness, and a sense of nervous instability similar to that in an epinephrine reaction frequently supervene. The convulsive seizures occurring in man after forty-five minutes' exposure (62) and in animals are well-known phenomena.

Bean & Whitehorn (63) report that oxygen at 5 atmospheres pressure produces bradycardia in the dog. With vagi intact the heart was slowed and the P-R interval prolonged as much as 40 per cent.

#### CARBON DIOXIDE

Carbon dioxide augments the toxic properties of oxygen (64, 65). Increased cerebral blood flow (60, 66, 67) and interference



with carbon dioxide transport are believed to be factors underlying this relationship. In unpublished experiments, however, we (Behnke *et al.*) have been unable to demonstrate any retardation in the elimination of carbon dioxide from tissues.

Carbon dioxide also intensifies the symptoms of nitrogen narcosis observed in deep sea divers (28) but a sharp differentiation between the effects of carbon dioxide and those attributable to nitrogen is not possible.

In aviation the importance of alveolar carbon dioxide tension in relation to blood pH (34, 35) has been mentioned; Dill (68) and others have demonstrated an increase in the tolerance threshold for low oxygen pressures associated with carbon dioxide inhalation.

#### ATMOSPHERIC NITROGEN

*Narcotic effect.*—Behnke *et al.* (69, 70) ascribe the neuromuscular disturbances and alterations in mood associated with exposure to atmospheres with high pressure to the narcotic effect of atmospheric nitrogen. Argon possesses a similar property (71); helium, on the other hand abolishes or renders negligible the narcotic-like retardation. In the light of the Meyer-Overton hypothesis the following oil-water solubility ratios are of interest (71).

SOLUBILITY COEFFICIENTS OF GASES IN OIL AND IN WATER AT 38°C.

	Nitrogen	Argon	Helium	Oxygen
In olive oil	0.0667	0.1395	0.0148	0.0113
In water	0.0128	0.0262	0.0087	0.023
Ratio.....	5.24:1	5.32:1	1.7:1	5.0:1

*Nitrogen elimination curves; cutaneous diffusion of nitrogen.*—Behnke & Willmon (39) measured the nitrogen diffusing from the body during the inhalation of oxygen for periods of seventeen hours; nitrogen elimination was complete within the limits of experimental error at the end of about nine hours, this fact corroborating previous determinations (72). In these experiments the passage of atmospheric nitrogen through the intact skin was demonstrated.

#### HELIUM

The low density of helium compared with nitrogen rendered this gas valuable for the treatment of obstruction in the tracheo-



bronchial tree (73) and in anesthesia (74). Reference has been made to its employment to relieve blockage in auditory tubes (25, 26, 27).

Respiratory resistance of helium and nitrogen has been measured by Barach (73) and others (71). Dean & Visscher (75) separate resistance to ventilation into viscous and elastic components. Substitution of helium-oxygen mixture for air produced no change in viscous resistance.

In diving operations helium-oxygen mixtures have made possible descents to depths hitherto impossible of attainment by reason of removal or diminution of the narcotic effects of nitrogen (71, 76, 77, 78).

*Helium elimination curve; solubility in body tissues.*—From three to five hours are required for the complete elimination of helium from the body (39), or about one half of the time required for nitrogen. Exercise increases helium elimination 60 per cent during the first fifteen minutes; the accelerative effect of exercise is not appreciable after the first thirty minutes. The helium capacity of saturated body tissues is about 40 per cent of the nitrogen content, largely by reason of lower solubility in fat (39).

*Cutaneous diffusion of helium.*—Behnke & Willmon (79) found that helium diffuses at a sufficiently rapid rate through skin to permit the measurement of peripheral blood flow. Values obtained are in agreement with the determination of cutaneous blood flow by Hardy & Soderstrom (80), and Gagge (81) on the basis of heat conductance.

#### APPLICATION OF STUDIES IN DEEP SEA DIVING: WORK IN COMPRESSED AIR

*Submarine disasters.*—In the rescue and salvage operations incident to the *U. S. S. Squalus* disaster, wide application was made of the physiologic studies enumerated in the previous paragraphs (4, 28). The narcotic effect of atmospheric nitrogen augmented probably by the increased concentration of carbon dioxide rendered work both inefficient and dangerous at depths of 240 feet. It can be said that without the employment of helium-oxygen mixtures for diving, salvage operations would not have been possible. In the recent *U. S. S. O-9* disaster, divers in a helium-oxygen atmosphere reached new depths of 440 feet in the open sea (77).



The time required for decompression of divers following short exposures is about the same whether the divers atmosphere is air or helium-oxygen (39). For saturation exposures in a helium atmosphere, however, the time required for decompression has proved to be about one third of the time required for the saturation exposure in air. Undoubtedly the decreased solubility coefficient of helium in fat compared with nitrogen greatly lessens helium uptake by the bone marrow in which tissue "bends" are believed to have their origin.

*Oxygen therapy.*—The employment of oxygen for the prevention and treatment of decompression embolism constitutes a notable advance. The physiologic studies of Behnke & Shaw (82) have served as the basis for the treatment of divers at the Experimental Diving Unit (83) and during diving operations in connection with the *U. S. S. Squalus* disaster (28). Prolonged recompression for twelve hours or longer at comparatively low pressures has been especially effective (83).

In both the American and British Navies oxygen is used routinely to accelerate elimination of inert gas during the later stages of decompression, i.e., below the sixty-foot level.

Jones *et al.* (50) report beneficial results in the use of oxygen during decompression of workers in Hudson tunnel operations.

*Surface decompression.*—The practice of bringing divers rapidly to the surface and of completing decompression in a chamber aboard ship proved to be successful (28). In this procedure advantage is taken of the latent period required for the growth of bubbles to produce widespread embolism.

*Osseous lesions in compressed air illness.*—Although statements are frequently made to the effect that the symptoms of compressed air illness arise from extravascular bubble formation, clinical and laboratory observations render the gas embolism theory more probable (61).

Consideration of the structure of bone with its medullary marrow high in fat content, its peculiar arrangement of blood vessels, and the extraordinary sluggish circulation, makes it probable that this tissue is highly susceptible to formation of gaseous embolism following rapid decompression. "Bends" comprising pain and sometimes temporary disability, are the clinical expression of the presence of emboli sufficient in number to cause anoxia.



Of great interest, therefore, are recent reports of characteristic bone lesions observed in compressed air workers (84, 85, 86). Confirmation of the etiology of these lesions, however, awaits animal experimentation. We have not observed similar changes in the bones of deep sea divers. Either repeated embolic injury is required to bring about the altered morphology or some concomitant factor as infection must also be present.

*Hemoconcentration and shock in compressed air illness.*—The presence of air embolism in dogs is usually complicated by the development of hemoconcentration and certain characteristics of the picture of shock (37, 82). Plasma loss through capillaries damaged by anoxia is believed to underlie the etiology of the hemoconcentration.

### MILITARY AND INDUSTRIAL PROBLEMS

The division of Medical Sciences of the National Research Council is initiating and conducting physiologic investigations to the end that military personnel will be better able to cope with adverse environments and conditions characterized by severe temperature changes, noise and vibration, overcrowding, infection of the upper part of the respiratory tract, and the various psychological and somatic factors that give rise to the fatigue state.

It is unfortunate that the considerable advances made under the impetus of a national emergency, because of their military value, are not yet available for review.

*Health of the Navy.*—As an indication of morbidity of a select group of men, naval statistics reflect the effect of variability in the environment.

From the latest annual report of the Surgeon General of the Navy covering the calendar year 1939 (87), 61,000 new admissions to the sick list are recorded giving a rate of 408.37 per thousand as compared with 477.03, the median for the preceding nine-year period. There were 1,201,718 sick days or an average of 19.67 per admission, 2.2 per cent of all personnel were constantly on the sick list throughout the year.

*Problem of infection of the upper part of the respiratory tract.*—Disease spread by direct and indirect transfer of infectious secretions or discharges from the mouth or nose and included in the category of colds is a leading cause of morbidity.

If catarrhal fever or the common cold, acute and chronic



tonsillitis, and influenza are grouped together, then these maladies comprise 30 per cent of all admissions, and 11.5 per cent of total sick days. Apart from overcrowding the question of the effect of rapid changes in environmental temperatures is paramount as a predisposing cause in this type of infection.

*Effect of climatic changes.*—The reports of Petersen, Huntington, and Mills stress the importance of climatic influence on body economy. The known physiologic adjustments underlying climatic adaptation, or failure to maintain a high energy level, however, have not been impressive and can be summarized essentially as an altered blood distribution in response to ambient temperature fluctuations (88). It does not appear likely, moreover, that the actual quantity of blood diverted from the internal organs is sufficient for example, to account for the deterioration observed in hot humid climates. The theory of Mills that adrenal function may be impaired is supported by many of the observed symptoms, yet obviously it is not amenable to lucid proof.

Mills (89) has enumerated the dangers inherent in the transfer of military personnel from tropical to temperate or semifrigid climates particularly with reference to susceptibility for respiratory infections. The seasonal incidence of respiratory infection is in accord with the concept that climatic factors are predisposing or underlie susceptibility.

*Preventive measures against infection of the upper part of the respiratory tract.*—The matter of how best to protect personnel from severe ambient temperatures by means of suitable clothing is now under investigation.

The basic problem of destroying the infectious agents has centered in recent years around the work of Wells (90, 91) and the use of ultraviolet irradiation. Mundo & McKhann (92) have reported a decreased incidence of respiratory infection in infants housed in cubicles treated on top and in front with ultraviolet radiation.

The value of the application of ultraviolet radiant energy directly to the body especially to protect against the common cold is still controversial (93). In the military service, the prophylactic treatment with ultraviolet irradiation of aviators engaged in high flying, or submarine personnel, and of troops in arctic or subarctic areas is under consideration.

*Physiological principles in heating and ventilation.*—The



chapter on physiological principles in the *Guide* published by the American Society of Heating and Ventilating Engineers (94) summarizes investigations applicable to field practice. As a criterion of minimum outdoor air requirement, the presence of objectionable body odor rather than the concentration of carbon dioxide, is a better index (95).

With reference to the factors of temperature, humidity, and air motion, Ferderber & Houghten (96) review the effective temperature index and its application to ordinary living and working environments in winter and summer. In contrast with the "effective temperature" scale derived on sensory basis, "operative temperature" represents a calorimetric scale defining the equivalent environmental temperature with which a warm body exchanges heat at a standard cooling rate, as usually applied. Operative temperature combines an average of air and wall temperatures weighted according to their relative effectiveness as described by radiation and convection constants. The applicability of this concept as stated by Gagge (81), and developed from the numerous researches on partitioned calorimetry in Winslow's laboratory, remains to be determined in field practice.

*Hot atmospheres.*—Basic studies by Yaglou, Dill, Talbott, Houghten, and Fleischer have defined limiting temperatures in industry and have led to the employment of restorative measures of proper fluid and salt intake.

Houghten, Rosenberg & Ferderber (97) in their study of the seasonal variation in reactions to hot atmospheres found that the increase of body temperature and pulse rate was greater in winter than in summer on exposure to identical degrees of heat for the same period of time. No greater sweat secretion was found in summer as compared with the winter tests.

In estimations of the blood volume of men exposed to hot atmospheres for a few hours so that heat loss was entirely dependent upon evaporation, Glickman, Montgomery, Hick & Keeton (98) concluded (a) that the plasma volume could increase by withdrawal of fluid from body reservoirs, (b) that a decrease could occur as a result of evaporation of blood plasma, and (c) that a constant plasma volume could be maintained if the responses of (a) and (b) were balanced.

Of considerable importance is a comparison of the physiologic effect of a hot dry atmosphere (100°F. dry bulb, 38 per cent



relative humidity) with a hot wet atmosphere (87.5°F. dry bulb, 83 per cent relative humidity), both having the same effective temperature index. With respect to these atmospheres Lee & Boissard (99) found that replacement of water lost during exercise was effective in preventing excessive rise in pulse rate.

Behnke (100) has recorded a relationship between the Schneider index and the ambient temperature in a group of men living in a compartment of a warship four hours daily and transported from Peru to California. Essentially there was an increase in pulse rate in the warm atmosphere attributed to greater cutaneous blood flow, and a fall in systolic blood pressure. Body temperature was elevated about 0.6°F. in the tropical compared with the temperate climate.

In the hot humid environment acclimatization is attended by an increase in blood volume and a higher pulse rate. The increased flow of blood to the skin interferes with adequate cardiac output (101).

In view of the increased peripheral circulation when the body is in the zone of evaporative heat regulation, the role of posture is of considerable practical interest. Nielson, Herrington & Winslow (102) found that a passive change of posture from horizontal to a semi-inclined position with feet lowered, produced a peripheral vasoconstriction and a rise in internal body temperature in subjects not adapted to warm environments. In experimental heat exhaustion particular attention was paid to the role of posture in relation to peripheral circulatory failure by Keeton, Hick, Glickman & Montgomery (103).

It follows from these investigations that change in posture from the upright to varying degrees of the recumbent position and with periodic elevation of the feet will serve as a practical measure to reduce cardiovascular strain and fatigue in hot environments.

Two other measures investigated by Mills (104) to counteract the debilitating influence of heat are provision for cooling, and the administration of accessory food substances as vitamin B<sub>1</sub>.

*Effect of cold.*—The comprehensive analysis and survey by Yaglou (105) summarizes our present knowledge with respect to the effect of temperature extremes on workers in industry.

In the service, aviators may be exposed to temperatures as low as -50° F. When current studies now in progress in Canadian



laboratories by Burton and Bazett become available, a great advance in this field of applied physiology is certain.

Electrically heated underwear was used to keep deep sea divers warm in connection with the salvage operations on the *U. S. S. Squalus*. Loss of body heat by conduction was considerably greater in the helium atmosphere than in air.

*Artificial respiration and inhalation.*—Henderson & Turner (106) discuss methods of artificial respiration and reaffirm previous conclusions with respect to factors of muscular tonus, carbon dioxide inhalation, and the danger inherent in the employment of mechanical respirators operating on the suck and blow principle.

Hooker, Kouwenhoven & Langworthy (107) concluded that the volume of air moved by manual application of abdominal compression applied to the subject in the vertical position was greater than with the Schaefer method. Behnke (108) found that compression of the diaphragm in a conscious subject lying on his back was ineffective in pushing out supplemental air. With the subject on his side, however, the same maneuver appreciably aided expiration. For inflation of the lungs with mechanical appliances, pressures of 10 to 15 mm. Hg were found to be adequate.

*Fatigue.*—The survey of industrial fatigue by Dill, Bock, Edwards & Kennedy (109) epitomizes our present knowledge of the subject. A sharp distinction is drawn between the psychologic and the physiologic aspects of the problem. It is the former consideration that is so perplexing in the military service where apparently healthy men become useless for certain hazardous types of duty as flying, without showing the usual physiologic manifestations of breakdown.

The recent comprehensive investigation of Jones, Flinn & Hammond (50) on fatigue in truck drivers serves as a good review of the difficulty of evaluating fatigue in terms of objective tests. Significant results were obtained in tests of motor function involving speed of tapping, reaction-coordination ability, and degree of body sway. Of the ocular tests, glare resistance and measurement of saccadic eye movements by Specht showed significant changes with relation to hours of driving.



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## THE PHARMACOLOGY OF DRUG ADDICTION

BY M. I. SMITH

*Division of Chemotherapy, National Institute of Health,  
Bethesda, Maryland*

This is an attempt to review the literature of the past three years pertaining to the pharmacology of such drugs as are commonly considered to be habit forming. No sharp line is drawn here between drugs capable of inducing addiction and physical dependence and those merely capable of inducing habit formation. The present review will be limited to a discussion of those pharmacologic aspects of morphine and derivatives, alcohol, cocaine, the barbiturates, amphetamine, acetanilide, and cannabis only insofar as they may directly or indirectly concern the problems of tolerance, addiction, and habit formation.

Of the more recent previous reviews of immediate interest the following should be mentioned: (a) a discussion of the theory of drug addiction by Tatum & Seevers (1); (b) a classification of addicting drugs with a comprehensive discussion of the theories of tolerance, mechanism of withdrawal syndrome, and the underlying basis for different modes of treatment by Adams (2); and (c) a review of the pharmacology of barbiturates by Tatum (3) including a brief discussion of the literature on tolerance and cumulation (4).

### OPIUM ALKALOIDS AND DERIVATIVES

*General.*—The incidence of drug addiction is indicated in the British Government report to the League of Nations for 1937 showing that 72 per cent of the cases were addicted to morphine, 17 per cent to heroine, and 8.5 per cent to cocaine (5a). A United States Government survey of the state of Michigan for 1938 with a population of 4,830,000 indicates an incidence of seventeen addicts per 100,000 (5b). Chopra (6) estimated that there were 25,000 opium addicts in Bengal, some 2,000 to 4,000 cocaine habitues, and fully 25,000 addicted to Indian hemp.

In a study of body build in four hundred drug addicts, Brown (7) found that they were average or slightly superior in height and weight, and that their body build as a group was within normal limits. Addiction, therefore, could not be ascribed to gross consti-



tutional weakness. The postural sway test in adult whites according to the observations by Vogel (8), showed that addicts are more suggestible than nonaddicts, this hypersuggestibility fading with or after withdrawal of the drug.

Contrary to the earlier conclusions by Light and associates (9) that morphine addiction is not characterized by physical deterioration or impairment of physical fitness aside from addiction *per se*, Cole (10) reported abnormal pulmonary roentgenographic findings in more than 85 per cent of drug addicts; hypertrophic or atrophic emphysema was present in the majority of the cases. Cole ascribes these findings to a pharmacodynamic action of morphine on the pulmonary circulation similar to that previously shown by Brunnelli's experiments, in which large doses of morphine in cats led to a fall in arterial blood pressure, a fall in the pressure of the left atrium, and a rise in pulmonary pressure with an increase in liver and lung volume (11). These effects may be due to changes in capillary permeability and in the osmotic pressure of the pulmonary colloids resulting in the absorption of water in the pulmonary vein.

Muscular contractile power has been studied in opium addicts by To (12). Ergograph and dynamometer measurements showed that the right grasping power in addicts was stronger than the left and that males were stronger than females, as in nonaddicts. The contracting power of the dorsal muscles of the arm in addicts was weaker indicating the presence of a lowered bodily force in addition to a poorer physical constitution.

The effects of morphine and derivatives on the gut have been studied by Myers in cats. Morphine usually produced a diminution in tone and in frequency and amplitude of movements of the stomach (13) with an increase in tone and peristaltic movements of the small intestine and ileocolic sphincter (14). An increase in tone of the rectum was also noted (15). Heroin and dilaudid (dihydromorphinone) had similar effects but more intense, while codeine, dicodid, and eukodal were generally less active. Myers (16) concluded that the constipating action of morphine and derivatives is explainable on a mechanical basis. His experimental data suggest that dilaudid is likely to be a constipating drug, though less so than morphine, while dicodid and eukodal are probably not. Noda (17) reported experiments indicating that the inhibiting action of morphine on the intestine of the rabbit and cat



*in situ* is effected by the splanchnic nerve through the intermediation of epinephrine liberated in the suprarenals.

Recent studies on the effects of morphine and derivatives on basal metabolism (18) indicate that they all lower the metabolic rate in rabbits, the action of heroine being greater than that of morphine and this greater than codeine (19). Papaverine and narcotine had slight effect, while pantopon was very active, presumably due to its morphine content and the synergistic action of this with the other ingredients of pantopon (20). Contrary to these results, Barbour, Porter & Seelye (21) reported experiments in morphine-tolerant dogs indicating that morphine is a metabolic stimulant, and that the degree of stimulation appears unrelated to the presence or extent of chronic morphinism. This stimulant action, they assert, is independent of neuromuscular activity.

The influence of opium alkaloids on acid-base balance and gaseous metabolism of rabbits was studied by Ra (22). Acidosis was produced by the alkaloids of the phrenanthrene group and slight alkalosis by the members of the isoquinoline group. The effects on blood gas metabolism were related to the action of the drugs on the respiratory center: those depressing the center resulted in an accumulation of carbon dioxide and diminution of oxygen, while the alkaloids stimulating the respiratory center produced the opposite effect. In the first instance the effects are believed to be produced through vagus stimulation, and in the latter through the medium of sympathetic stimulation. In chronic poisoning with morphine, heroine, and pantopon the acidosis was gradually diminished and disappeared when tolerance was established. Disturbed acid-base balance persisted in chronic poisoning with papaverine.

The effects of morphine on temperature of rabbits were examined by Ko (23), who found that 5 to 200 mg. per kg. produced hypothermia in normal rabbits, this decreasing to disappearance with repeated administration of the drug and reappearing upon sudden suspension of the drug. The latter is considered a manifestation of abstinence. Hemingway (24), however, found a slow fall in the temperature of the dog preceded by a rapid rise after a subcutaneous injection of 10 mg. per kg. morphine. His experiments seem to indicate that morphine sensitizes the hypothalamus.

Observations on blood concentration in morphine addicts were reported by Williams (25). Examination of the hematocrit, specific



gravity, and water content in a series of addicts indicated hydration during addiction. During withdrawal, temporary decrease in hydration occurred but in no case a true concentration. This is contrary to the results previously reported by Light and associates (26, 27), and is in agreement with the experimental results by Barbour and associates, who reported hydration in tolerant dogs (28), this being explained on the basis of high environmental water exchange (29).

Ko (30) studied the effects of autonomic drugs on blood calcium and potassium in normal and tolerant rabbits and found these enhanced in chronic morphinism, these facts indicating an increased susceptibility of the autonomic nervous system in tolerant animals.

The effects of morphine and derivatives on blood sugar were studied by Emerson & Phatak (31), who, confirming the earlier work of Ro (32), showed that the hyperglycemic response to morphine in rabbits is diminished and gradually reversed on repeated injection, and may reappear on withdrawal. Dilaudid gave the same results.

Mei, Ito & Matuo reported on the cerebrospinal fluid in human morphinism (33). Its content in total protein, sodium chloride, lactic acid, and glucose was about the same in addicts and during abstinence in addicts as in normal individuals. Higher pressures and a greater ratio of globulin to albumin were found in addicts. Cholesterol was absent in addicts or during abstinence.

An analysis of the effects of opium alkaloids on pain threshold was reported by Wolff, Hardy & Goodell (34). Using a new quantitative method for measuring pain thresholds in the human skin by thermal radiation (35), the authors compared the effects of morphine, codeine, dilaudid (dihydromorphinone), metopon (methyl-dihydromorphinone), and pantopon. The conclusion was reached that the therapeutic effectiveness of the opiates is dependent mainly on three properties: (a) the threshold-raising action, (b) the dissociation of pain perception from the usual reaction to pain, and (c) the induction of lethargy and sleep.

The lowered sensitivity of the skin of opium addicts to the intracutaneous injection of morphine was noted by Oh (36). Thus, with a concentration of 1:1,000,000 morphine hydrochloride, 9 per cent of the addicts gave a positive reaction and 72 per cent were negative, while in the control group 70 per cent gave a positive re-



action and only 3 per cent a negative reaction. The diagnostic value of this test is questionable.

The effects of opium alkaloids on electrical potentials of the cerebral cortex were studied in opium addicts by Andrew (37). The occipital alpha rhythm was high during addiction. An injection of a stabilizing dose of morphine or codeine increased the alpha percentage and decreased their frequency. This decrease is considered to be the effect of partial blocking of afferent impulses.

Ko reported a series of studies on the effects of opium and narcotic addiction on the female generative organs of experimental animals (38, 39, 40, 41), including the response of the excised uterus of chronically poisoned rabbits to various drugs (42), and on the gynecological disorders among opium and heroine human addicts (43).

The histopathology of the bone marrow in the course of morphine poisoning in experimental animals was described by Gaforeanu, Diaca & Soan (44).

New experiments on the toxicity of morphine and derivatives were reported as follows. A comparative study of the toxicity of dilaudid and morphine on intravenous injection in mice indicates that the former is 3.7 to 3.8 times as toxic as morphine (45). Rai (46) found that the toxicity of morphine in rats and guinea pigs born of chronically poisoned animals was such as to suggest that the continued treatment with morphine confers only a slight resistance upon the offspring. In a study of the relation of age to the toxicity of morphine Eddy (47) found that the average fatal dose in rabbits increased until about the twelfth week and decreased again from the twelfth to the twenty-fourth week. Moreover, the minimal convulsant dose of morphine was found to vary with age in a similar manner. The fatal dose of chemically related derivatives of morphine such as dihydromorphine, codeine, dihydrocodeine, isocodeine, pseudocodeine, and thebaine also varied with age but in a manner not strictly parallel with morphine. The question of modification of the action of codeine by acid radicals was examined by Strong & Poe (48). They injected intravenously the sulfate, salicylate, benzoate, and the *o*-nitro-, *o*-chloro-, and *o*-bromobenzoates of codeine in unanesthetized rabbits and recorded the effects on the respiration and blood pressure. The acid radicals had little effect on the intensity of action. In a study on the susceptibility of morphine-, cocaine-, or alcohol-habituated mice to



ether, Abreu & Emerson (49) found an increased resistance to ether in alcohol-treated animals but not in the morphine- or cocaine-treated groups. In these the susceptibility, if anything, was slightly increased. Glaubach (50) showed that the toxicity of morphine and codeine is increased, and their action prolonged and made more intense by sulfapyridine. The narcotic and toxic effects of papaverine had been found to be influenced by sulfapyridine in a similar manner (51). According to Nedzel, the toxicity of morphine to mice is greater on an acid diet than on an alkaline diet (52). On *Amoeba proteus*, Yo (53) found the tolerated concentration of heroine in a neutral medium was 0.25 per cent while 0.3 per cent was lethal. Cultivation of the amoeba for thirty generations in 0.15 per cent solution of heroine did not change the minimal lethal concentration; but when amoebae were grown in gradually increasing concentrations of the drug, they survived a concentration of 0.4 per cent. It would seem that slight tolerance to heroine can be acquired by the amoeba if the resistance is built up gradually. To test for abstinence the tolerant amoebae were placed in a heroine-free medium with no effects.

In tissue culture studies caffeine has been found to neutralize the damaging effects of morphine, codeine, heroine, eukodal, and papaverine (54). Tolerance of cells grown in tissue culture to the opium alkaloids was studied by Kubo (55, 56, 57) and by Sasaki (58). Fibroblasts and iris epithelium grown on a medium containing morphine sulfate soon recovered from the initial injurious effects and gradually acquired a tolerance. Sudden removal from such a medium caused degenerative changes which could be prevented by transplanting to a morphine-containing medium. Tolerance to heroine and codeine could be induced with equal ease, but not to eukodal (56).

The much debated question of addiction to codeine is discussed by Ostromislensky (59). According to his clinical experience, addiction to codeine will develop within about sixty days of continuous treatment with one-fourth to one-half grain three times a day. In such cases withdrawal symptoms invariably appear, though somewhat later than in morphinism. Himmelsbach (60, 61) confirms this opinion pointing out the probable reasons for the low incidence of codeinism: (a) the low euphoric effect, (b) the greater cost of addiction-sustaining amounts of the drug, (c) the relatively low solubility and relatively large doses required, which make the admin-



istration of the drug inconvenient. In this connection it may be recalled that SeEVERS (62) failed to induce addiction to codeine in monkeys, while Himmelsbach and associates succeeded in inducing tolerance to codeine in rats (63).

*Destruction and excretion.*—The ability of the liver of normal and tolerant rabbits to destroy morphine was studied by Ko (64) making use of the perfusion technique of the surviving liver. From the perfusion blood of tolerant animals 90 per cent of added morphine was recovered; 70 to 80 per cent was recovered from the perfused liver of nontolerant animals and only 53 to 67 per cent from the perfused tolerant liver. It was concluded that neither normal nor tolerant blood can destroy morphine, and that the normal destroying ability of the liver is augmented with addiction. Kuwahara's experiments, using an *in vitro* technique, failed to support these conclusions, as he was able to recover as much morphine from the liver of the tolerant rabbit as from the nontolerant after incubation with morphine added in constant relationship to the quantity of liver substance (65). The liver of rabbits during abstinence destroyed morphine *in vitro* at the same rate as the liver of tolerant rabbits during treatment (66). Inoue (67) examined the *in vitro* morphine-destroying ability of the liver in six different animal species and found this was not related to their natural tolerance to morphine. Hinohara (68) failed to demonstrate any destruction of morphine in either the blood or muscle of tolerant or nontolerant rabbits when incubated with the drug *in vitro*, and Kuwahara (69) could find no difference in the amount of morphine recoverable from the blood and liver of tolerant or nontolerant rabbits one hour after the subcutaneous injection of 200 mg. per kg. of morphine sulfate. In conformity with this, Yoshikawa's experiments on the elimination of morphine in the urine and feces in several different animal species after a single subcutaneous injection showed nearly the same rate of destruction in all species regardless of their natural susceptibility to the drug (70).

Recent work on the elimination of morphine may shed new light on the mechanism of tolerance and addiction. Pierce & Plant (71) had failed to find significant differences in the elimination of morphine in tolerant and nontolerant dogs. Their experiments, which determined free morphine alone, indicated an average total output of about 12.5 per cent of the intake in both cases. Endo, however, has pointed out that morphine may be excreted in the



urine both in free and bound forms. He has shown that more morphine can be recovered from the urine of treated rabbits after hydrolysis with .025  $N$   $H_2SO_4$  for two hours (72). Moreover, such urine contained an increased amount of glycuronic acid, and it is suggested that in chronically poisoned animals the functional capacity of the liver to detoxify morphine by conjugation is augmented. Oberst, using improved analytical methods (73), studied the urinary excretion of morphine in a series of human addicts who had been stabilized on a minimum amount necessary for the maintenance of physiological equilibrium. The daily dose given subcutaneously varied from 45 mg. to over 4 gm. The urinary morphine was determined before and after hydrolysis. The average daily output of free morphine in the urine was only 4.4 per cent of the intake; while the total output, as determined after hydrolysis, was in some instances as much as thirty-six fold, thus demonstrating the existence of at least two forms of morphine in the urine of the addicts (74). Gross & Thompson (75) have arrived independently at similar conclusions. Their experiments on dogs showed that morphine is excreted in the urine in free and combined forms. Significantly, they point out that by this method 80 to 92 per cent of the total dose given is recoverable from the urine of the nontolerant dog, whereas in the tolerant dog only 35 to 66 per cent is recoverable, this fact indicating a greater destruction of the drug in the tolerant animal. Moreover, the greater portion of recoverable morphine in the nontolerant dog is combined, while in the tolerant dog only 30 to 50 per cent of the recoverable morphine is combined. This would suggest a more effective conjugation-detoxifying mechanism in the nontolerant animal. In a more recent study Thompson & Gross (76) recognize four different types of morphine in the urine of treated dogs: (a) free; (b) easily hydrolyzable at pH 1 to 2 for two hours at  $100^\circ C.$ ; (c) a more stable fraction, hydrolyzable in 5 per cent concentrated hydrochloric acid in the autoclave at 15 pounds pressure for 30 minutes; and (d) an unrecoverable fraction which is either destroyed or lost. A comparison of these four fractions in tolerant and nontolerant dogs showed that the free fraction was about the same in both cases, some 20 per cent of the amount administered, in conformity with earlier work (71). The easily hydrolyzable fraction constituted 8 per cent in the nontolerant and 16 per cent in the tolerant animal. The more stable fraction amounted to 66 per cent in the nontolerant and only 29 per cent in the tol-



erant. And finally the unrecovered fraction was only 6 per cent of the dose administered in the nontolerant and 35 per cent in the tolerant dog. The peak of morphine excretion was more readily reached in the tolerant animal, in which the residual morphine was mostly free; while in the nontolerant, it was for the most part in the form of the more difficultly hydrolyzable fraction. All this seems to indicate more destruction in the tolerant animal and a higher rate of conjugation in the nontolerant, suggesting a more efficient detoxifying mechanism.

The relation of urinary excretion to dosage in human addicts with different narcotics and different routes of administration was studied by To & Ri (77), who found 27 to 29 per cent of the dose administered excreted, whether morphine or opium, if administered orally, and 50 to 60 per cent when given subcutaneously. Oberst reported an excretion of only 5.4 per cent for morphine and 5.9 per cent for codeine when given subcutaneously and 2.7 per cent and 4.3 per cent respectively when given orally (78). In earlier work a constant ratio of urinary morphine output to that given had been found by Fry and associates (79) regardless of the amount given, the per cent excreted being approximately 10. No attention was paid to the possibility of the narcotic being excreted in different forms in these experiments and these data may have to be revised.

*Enzymes.*—Studies on the effects of opium alkaloids on blood and tissue catalase in rabbits were reported by Cho. A single injection of morphine (80), heroine (81), or codeine (82) increased the blood, liver, kidney, and muscle catalase, while repeated injections resulted in a gradual disappearance of this increase, and this is regarded as a manifestation of tolerance. Using this as a criterion of addiction, Cho showed that rabbits made tolerant to morphine exhibited addiction to members of the phenanthrene group but not to those of the isoquinoline group (82), and conversely, animals chronically poisoned with papaverine showed some degree of tolerance for narcotine but not for the members of the phenanthrene group (83).

A study of the effects of morphine on respiratory enzymes revealed inhibition of lactic, citric, and glucose dehydrogenases but not succinic or alcohol dehydrogenases. Codeine and thebaine had no effect. The oxygen uptake of rat's brain without added substrate was not affected by morphine but was regularly inhibited in



the presence of lactate and in some preparations also in the presence of glucose, pyruvate, and  $\alpha$ -ketoglutarate (84).

An enzyme in rabbit serum capable of deacetylating heroine was reported by Wright (85). Individual sera varied in their ability to split off the phenolic and alcoholic acetyl groups. Sera of rabbits capable of removing both groups deacetylated monoacetyl morphine and removed the phenolic acetyl group from diacetyldihydromorphine. Sera of rabbits capable of removing only the phenolic acetyl group from heroine did not hydrolyze monoacetylmorphine and only slowly removed the phenolic acetyl group from diacetyldihydromorphine. It is believed that the potency of certain morphine derivatives may be determined by the presence of deacetylating enzymes. The possibility that such an enzyme is concerned with detoxification seems a more likely explanation since, as is well known, the acetylated derivatives of morphine are more toxic than the parent substance.

The effects of morphine and derivatives on cholinesterase have been the subject of considerable study. The matter deserves careful attention for it appears to promise new light on the mechanism of action of the opium narcotics. Bernheim & Bernheim (86), using the isolated guinea pig ileum for their tests, were able to demonstrate a depressing effect of morphine on brain cholinesterase *in vitro*. Later Kuhn & Surles (87) confirmed this and extended these observations to codeine, dilaudid, and dionine. They attempted to correlate their results with the central emetic action of the opium alkaloids. The sensitizing ability of narcotics on leech muscle to acetylcholine was found by Dastague & Bresson for codeine and morphine to be 1:50,000, for heroine 1:1,000, and for eukodal (dihydrohydroxycodine) 1:50 million (88), or of about the same order of activity as physostigmine (89). Slaughter & Lacky (90), measuring esterase activity by the method of Hall & Lucas (91), were unable to demonstrate an inhibiting action by morphine *in vitro* but were able to show a 20 per cent reduction in cholinesterase activity in the serum of dogs twenty minutes after a subcutaneous injection of 5 mg. per kg. morphine. This is considered as evidence of the cholinergic action of morphine. Confirmatory evidence has been presented by Eadie, who showed by a continuous titration method the inhibition by morphine of hydrolysis of acetylcholine when added to dog serum (92). The rate of inhibition under varying conditions of enzyme, substrate, and inhibitor was such as to



suggest competition for enzyme by substrate and inhibitor rather than the destruction of the catalytic activity of the enzyme by the inhibitor.

The pharmacological and therapeutic applications of the foregoing findings are emphasized by Slaughter and associates. Similar to the earlier experiments of LaBarre (93) showing potentiation of morphine by choline on the excised intestine, Slaughter & Gross (94) were able to demonstrate a potentiating effect of physostigmine on morphine with respect to its action on the gut, the cat's blood pressure, and toxicity in rats. The authors ascribe this to the cholinergic action of morphine due to its depressing effect of cholinesterase. The hyperglycemic action of morphine held to be due to the liberation of epinephrine does not necessarily oppose this view since acetylcholine has been shown to be concerned with the transmission of stimuli from splanchnic nerve terminals to the cells of the adrenal medulla (95). In further experiments Slaughter & Munsell (96) also demonstrated a potentiating action of morphine by prostigmine on the pressure-pain response in cats. This they found was antagonized by atropine. That this action is probably central is indicated by the experiments of Adam and associates in which stimulation of the hypothalamus in cats often as much as doubled the acetylcholine content of the cerebrospinal fluid (97). In a comparative study of a series of anticholinesterases with regard to their effects on the spinal cord of the cat and their influence on cholinesterase, Schweitzer, Stedman & Wright (98) found sufficient correlation to support the view that their central excitatory and depressant actions are due wholly or in part to their inhibiting action on cholinesterase. Contrary to this, however, Cortell, Feldman & Gellhorn (99) were able to inhibit cholinesterase by 50 per cent in a variety of experimental conditions with consequent increase in the acetylcholine content of the central nervous system without grossly disturbing its functions. Finally Slaughter, Parsons & Munal (100) applied their experimental results in the clinic and found that half the accepted dose of morphine combined with 0.5 mg. prostigmine methylsulfate produced as good relief as larger doses of morphine, without its constipating effect. They suggest that suitable combinations of these drugs may be useful in the treatment of opium addiction.

*Chemical structure and pharmacologic action.*—Much work has been done in the search for more effective substitutes for morphine.



In a recent report of the Health Organization of the League of Nations the collective studies on the comparative effects of morphine, heroine, codeine, dionine, eukodal, dicodid, dilaudid, and acedicon are discussed (101). The evidence adduced indicates that they all produce euphoria in varying degrees and they all present addiction liabilities.

The work done under the direction of the Drug Addiction Committee of the National Research Council has been ably summarized by Eddy (102). Numerous compounds were prepared, both as modifications of the morphine group with the latter as the starting point, and as newly synthesized compounds from unrelated or distantly related nuclei. These were studied for their effects in experimental animals, and some of the more promising ones were submitted for clinical trial. The effects of morphine derivatives obtained (*a*) by covering the phenolic or alcoholic hydroxyl groups with various substituents, (*b*) by opening the ether-oxygen bridge of morphine, and (*c*) by effecting a spatial shift of the alcoholic hydroxyl group were described by Small & Eddy (103). Mosettig & Eddy also reported on the synthesis and pharmacologic action of a series of derivatives of phenanthrene, dibenzofuran, and carbazole (104). These studies do not seem to permit many generalizations beyond the possibility of dissociating morphine-like properties by chemical changes, though the direction of change is not always predictable. Methylation of the phenolic hydroxyl group has usually resulted in decreased potency and prolongation of action, while the replacement of the alcoholic hydroxyl group by hydrogen or oxygen resulted in increased potency and shortening of action. Spatial shift of the alcoholic hydroxyl group gave irregular effects and saturation of the C<sub>7:8</sub> double bond tended to increase potency and duration of action (105).

In his studies on carbazole derivatives Eddy (106) found the amino carbazoles more depressant and slightly analgesic, while carbazole itself is only slightly depressant and not at all analgesic in the cat. This is interesting for carbazole is an imino derivative of dibenzofuran which may be regarded as the nucleus of morphine. 3-Aminocarbazole, according to Eddy, is less toxic and less emetic than 3-aminophenanthrene. Since earlier work had shown that among the phenanthrene derivatives the amino alcohols were the most active analgesics (107), Eddy examined the amino alcohol derivatives of carbazole and found them less toxic and less con-



vulsant in cats but more emetic than compounds derived from phenanthrene by the addition of analogous substituents (108).

Morphine and dinitrophenol have been used clinically together for the possible mutual effect on metabolism that each might have upon the other. Eddy & Sumwalt (109) reported on a study of dinitrophenylmorphine in cats. The compound was equally toxic, less analgesic and emetic, and more convulsant and depressant than morphine. It exhibited none of the dinitrophenol-like action. The authors disagree with the more favorable conclusions reached by Emerson & Phatak (110) and conclude that the poor solubility of this compound, its local irritant action, and greater depressant effect on respiration preclude its clinical use.

Clinical studies with the newer morphine derivatives and substitutes were also reported. Dilaudid (dihydromorphinone) was substituted for morphine in a series of addicts; it was about four times as potent as morphine and equally constipating and addictive, and it presented no therapeutic advantages over morphine (111). Desomorphine (dihydrodesoxymorphine-D) was found in human addicts to exhibit a high degree of addiction liability despite the relative freedom from tolerance and abstinence symptoms in experimental animals (112). Using the substitution technique, on the premise that a substance capable of satisfying and maintaining physical dependence can also produce it, Himmelsbach examined the addiction characteristics of (a) paramorphan (dihydromorphine), (b) desomorphine (dihydrodesoxymorphine-D), (c) desocodeine (dihydrodesoxycodeine-D), and (d) metopon (methyldihydromorphinone). Addiction was satisfied nearly completely with the first three and only partially with metopon (113). Lee (114) found the narcotic equivalent of metopon to be one half that of morphine (1/6 grain morphine being equal to 1/3 grain methyldihydromorphinone). Lee gives the following advantages for this compound: tolerance and dependence develop less rapidly than with morphine; the hypnotic effect is less marked and of shorter duration; it has fewer side actions; and unlike morphine, it is often possible to reduce the dose on readministration after temporary withdrawal. Dihydroisocodeine was compared with codeine by Davenport (115) in a series of advanced cases of tuberculosis with special reference to their effects on cough and bowel movements. No demonstrable superiority over codeine could be established, though it appeared less toxic, less convulsant, and more effective



in depressing the respiration than codeine in experimental animals (116). Lastly, fifteen of the most promising compounds previously studied were examined by Himmelsbach & Eddy (117) in morphine addicts; they were all found to possess addiction liability. This report appears to indicate that changes in chemical structure of morphine may alter the degree of addiction liability in the same direction with other pharmacologic properties, though not necessarily to the same extent.

*Withdrawal syndrome and treatment of opium addiction.*—Kolb & Himmelsbach (118) point out that the treatment of addiction should be based on a better understanding of its mechanism and a better knowledge of the pathologic physiology of withdrawal. Tolerance and physical dependence, they state, is self-limited, hence rapid withdrawal in the course of fourteen days or less is the method of choice. Supportive measures and small doses of codeine should be used. Diuretics and potassium thiocyanate were of no use. The withdrawal symptoms, such as sweating, diarrhea, vomiting, etc., they believe are due to stimulation of the sympathetic as a compensatory mechanism. Ossenfort (119) adhering to a similar program recommends bromides and phenobarbital as adjuvants, paraldehyde to combat restlessness, and 5 per cent glucose intravenously to combat diarrhea and excessive perspiration. So-called specifics, he states, have not proven satisfactory.

Chopra & Ganguly (120) advocate the use of lecithin and intravenous glucose injections. The latter is based on the earlier observations of a subnormal percentage of total protein in the serum of addicts (121) and of a low specific gravity of the blood and serum in tolerant dogs (28). The glucose is thus used to restore water balance. An increase in the euglobulins of the blood, they believe, suggests drainage of phosphate from the nerve cells, hence, the use of lecithin. Chopra & Chopra (122) claim to have treated two hundred cases with lecithin orally and glucose orally and intravenously with good results. Guha (123) confirmed the good results with this treatment in a smaller series of thirty-eight cases.

Of the various specifics rossium has claimed the most attention. Ostromislensky likened the shock stage which often develops in opium addicts to post-anaphylactic shock in experimental animals; and since rossium [bis (1-phenyl-3-methyl-5-pyrazolone)] had proved efficacious in experimental anaphylactic shock, its use in the treatment of drug addiction was advocated (124). Lambert



found this drug useful not only in the treatment of opium addiction, but also in allaying the nervousness and apprehension of patients recovering from acute and chronic poisoning with barbiturates and also in chronic alcoholism (125). However, Himmelsbach's carefully conducted clinical tests with rossium led him to conclude that it had no effect on the abstinence syndrome when used either alone or in combination with such other therapeutic agents as dextrose, barbiturates, or insulin (126). Frequent temporary subjective relief from dextrose alone is conceded.

A favorable effect on morphine abstinence symptoms in rats was claimed by Fitzhugh for thiamin (127). On the supposition that the heightened irritability of the nervous system during withdrawal might be due to thiamin deficiency, Fitzhugh administered to rats 5 mg. thiamin chloride subcutaneously before withdrawal of morphine with marked decrease in irritability. Himmelsbach (128) was unable to see any favorable influence in ten human addicts with thiamin chloride given subcutaneously in doses of from 150 mg. to 1 gm. per day for at least two days prior to abrupt withdrawal, and for two to four days after withdrawal. Moreover, the blood pyruvic acid which rises in thiamin deficiency was found by him within normal limits in the cases he studied. Cowgill (129) tested thiamin requirements in dogs made tolerant to morphine and was unable to obtain evidence to indicate that the anorexia in chronic morphinism might be due to vitamin-B<sub>1</sub> deficiency. The cocarboxylase content of brain, liver, and muscle, low in thiamin-deficient animals, was found not to be altered in chronic morphinism in rats according to Shideman & Seevers (130), and the degree of cocarboxylase reduction induced by thiamin deficiency was not modified in morphine tolerant rats.

#### COCAINE

The effects of chronic cocaine poisoning on liver lipids in mice were studied by MacLachlan & Hodge (131). Vacuolar fatty infiltration resulted from the feeding of 0.2 to 4.8 mg. per day for sixty days. The size of the liver was increased by 20 to 25 per cent over the controls, the neutral fat increased by as much as 778 per cent over the normal, and the cholesterol by as much as 148 per cent, while the phospholipid fraction remained unchanged. The changes observed suggest mobilization of the fats from their normal depots or some alteration in their metabolism.



The enzymatic action of cocaine has been studied by Keeser (132), who showed an inhibiting action on cholinesterase *in vitro*, and by Philpot (133), who found an inhibiting action on amine, cytochrome, and catechol oxidase but no effect on xanthine oxidase or malic and succinic dehydrogenases. Okumara (134) found an increased rate of respiration and glycolysis of mouse brain by cocaine.

A potentiating action for cocaine on the central nervous system of experimental animals has been reported for  $\beta$ -phenylisopropylamine (135). Matschulan & Amsler (136) were able to lengthen cocaine corneal anesthesia in rabbits by a preliminary subcutaneous injection of morphine, and Eicholtz & Krauth (137) found cocaine convulsions in rats to be augmented by morphine.

Enhancement of the vasoconstrictor action of cocaine by amino acids was reported by Ishihara *et al.* (138). Moller & Stefansson (139) found cocaine to augment the response of rabbits to the effects of epinephrine on blood sugar.

The anesthetic action of cocaine was found to be decreased in chronic oxalic acid poisoning, the effect presumably being due to a diminution of blood calcium (140). The antagonizing action of calcium would seem to be indicated in a report of the successful treatment of two cases of cocaine poisoning by the intravenous injection of a 10 per cent solution of calcium chloride (141). Paralysis by cocaine of intestinal villi seems indicated from the experimental evidence that it inhibits the absorption of glucose from the jejunum (142).

Langecker & Lewit (143) studied the detoxification of cocaine in several animal species by the intravenous injection of fractional doses at definite and short intervals. Its high rate of detoxification in the rabbit, they suggest, is due to demethylation to the less toxic benzoylecgonine and ecgonine.

Mice habituated to cocaine were reported to have no increased resistance to ether, while habituation to alcohol resulted in a decreased susceptibility (49).

#### THE BARBITURATES

Tolerance to barbiturates, though not as serious as with other drugs, is yet sufficient, according to Robinson (144), to require larger and larger doses which may ultimately lead to clinical evidence of toxicity. Excessive doses, he asserts, produce deteriora-



tion due to brain destruction. In 10 per cent of all the neurological cases admitted in his service in 1937 and 1938 he observed barbitol psychosis (145). The possible harmful effects from the indiscriminate use of barbiturates are emphasized in a series of cases reported by Drysdale (146). Important data on the barbiturate hazard are given by Hambourger in an analysis of hospital admissions during the decade 1928-1937 (147). In 643 cases of acute barbiturate poisoning the fatality rate was 7.3 per cent. The minimum fatal dose reported for barbital was 2 gm. and for phenobarbital 1.7 gm. The barbiturates in this series accounted for more than 10 per cent of all the addiction cases, excluding chronic alcoholism.

Thrombopenic purpura from therapeutic doses of sedormid (allyl-isopropene-acetylcarbamide) were reported by Hoffman (148) and by Moody (149).

In an experimental study on the repeated administration of large doses of amytal to dogs and monkeys over a period of two to six months, Swanson, Weaver & Chen (150) failed to see evidence of tolerance, withdrawal symptoms, or of decreased toxicity. At necropsy no pathologic lesions were found attributable to the drug. In agreement with this Schulte could find no evidence of dermatosis or visceral lesions in dogs or rats treated for over two months with a series of barbiturates including amytal, pentobarbital, phandorn, pentothal, and sedormid (151). Contrary results were obtained by Masuda, Budde & Dille (152), who were able to demonstrate an acquired tolerance in rabbits to amytal, pentobarbital, and pernocton. Their experiments suggest an increased rate of destruction of the barbiturate in tolerant animals. Similar results were obtained by Moir (153) in rats with nembutal and by Ettinger (154) in dogs with dial.

The problem of cross-tolerance between alcohol and some barbiturates was studied by Ahlquist & Dille (155), who showed that alcohol-tolerant rabbits were more resistant than normal rabbits to the depressant effects of pentobarbital and evipan.

Loewe (156) showed a synergistic action in mice between cannabis indica and pernocton (butylbromallyl barbituric acid). Cannabis, which had no hypnotic action, produced a marked increase in the hypnotic effect of the barbiturate when given simultaneously.

Tsuyusaki (157) examined the effects of a series of barbiturates on the blood pressure of the unanesthetized dog. There was a



transient slight rise followed by a fall in blood pressure. The lowest level paralleled the depth of anesthesia and recovery attended the wakening of the animal.

Clowes, Keltch & Krah1 (158) studied the extracellular and intracellular hydrogen ion concentration in relation to anesthetic efficiency of the barbiturates. Using the rate of cell division and oxygen consumption of fertilized *Arbacia* eggs and the inhibition of movement of *Arbacia* larvae as a measure of anesthetic activity they found a partial though incomplete parallel between the order of decreasing anesthetic effectiveness, the order of decreasing oil-water distribution coefficients, and the order of increasing solubility in water.

The factors concerned with the increased duration of barbiturate anesthesia produced by liver injury (159, 160) were studied by Tatum, Nelson & Kozelka (161). They found the lengthening of amytal anesthesia by morphine and carbon tetrachloride related to the degree of impairment of liver function and the simultaneous decreased rate of disappearance of amytal from the blood stream. The lowered functional capacity of the liver produced by morphine is believed due to reduced blood supply and that produced by carbon tetrachloride to direct liver injury. The effect of both drugs on the rate of disappearance of amytal is thought to be due to the impaired detoxifying function of the liver.

#### ACETANILIDE

Clinical chronic acetanilide poisoning with addiction was reported by Mackintosh (162). Cases are presented demonstrating the possibility of addiction to acetanilide if taken over a period of several years. It is asserted that addiction parallels tolerance to the drug which may be followed by withdrawal symptoms. Morgan & Anderson (163) reported a case of chronic acetanilide poisoning with cyanosis, which they attributed to methemoglobin and sulfhemoglobin produced by oxidation products of the drug. These authors prefer the term habit to addiction in the instance of acetanilide habituation. Reissman (164) reported a case of hemolytic anemia with cyanosis from chronic acetophenetidin (phenacetin) poisoning following the daily intake of 5 gm. of the drug over a period of seven years.

Experiments on chronic acetanilide poisoning in monkeys were reported by Smith (165). No effects were noted in animals receiving



100 mg. per kg. daily for eight to nineteen weeks, while animals receiving 500 mg. per kg. per day, about 150 times the average therapeutic dose in man, developed anemia of the hemolytic type with the conversion of some of the hemoglobin to a non-oxygen combining form. Tolerance with respect to the depressant effect of the drug was noted but none to its analgesic action. Acetanilide and phenacetin given daily in large doses up to 30 per cent of the fatal dose for thirty days produced methemoglobinemia and sulf-hemoglobinemia in rats and monkeys. Sodium bicarbonate afforded no protection against the blood dyscrasia (166).

#### AMPHETAMINE (BENZEDRINE)

Addiction to amphetamine was reported by Friedenberg (167) in a case of obesity in which the drug was taken first in 5 mg. and later 10 mg. doses twice daily for several months.

The clinical use of amphetamine in obesity is illustrated by a series of cases by Lesses & Myerson (168). According to these authors the drug is especially useful in anhedonia, a neurosis characterized by excessive ingestion of food indulged in as a means of compensation for disturbed mood. The drug lessens appetite and increases the sense of well-being. Ten to 30 mg. per day were used for six to twenty-five weeks with good results and no evidence of toxic manifestations or signs of tolerance. Similar results were reported by Rosenthal & Solomon (169), who suggest that the action of amphetamine in weight reduction may in part be explained by increasing diuresis and thus preventing the retention of excess water in the tissues.

Myerson, Loman, Rinkel & Lesses (170) showed that amphetamine is effective in preventing or counteracting the narcosis produced by the intravenous injection of sodium amytal and they advocate its use in overcoming severe side actions of barbiturate narcosis. Though pharmacologically amphetamine and barbiturates are antagonistic, Myerson (171) has emphasized their reciprocal effects by virtue of which they may mutually potentiate each other, especially where large doses of either are indicated. Thus in epilepsy large doses of barbiturates may be better tolerated if administered with small doses of amphetamine (172). In like manner amphetamine may be used more safely in the treatment of obesity if combined with suitable doses of barbiturates (171). In line with the experimental work of Michelsen & Verlot (173) in which animals



could be protected from deleterious effects of a lethal dose of avertin by a preliminary intramuscular injection of amphetamine, Boyd (174) injected intravenously 10 mg. amphetamine sulfate in a series of children immediately after operation for which 160 mg. per kg. avertin had been used for anesthesia. Immediate return of superficial reflexes, improved pulse volume, elevation in blood pressure, and reduction in the postoperative sleep were noted.

The present day therapeutic applications of amphetamine and a consideration of the pharmacologic actions upon which these are based are reviewed by Reifstein & Davidoff (175). They point out the drug is habit-forming in some individuals, much as alcohol is, and that its continued use leads to tolerance. The reaction pattern to this drug is variable and unpredictable. They consider the drug useful in narcolepsy, myasthenia, Parkinson's disease, barbiturate intoxication, alcoholism, and in morphinism where it seems to counteract the withdrawal symptoms. Its use in psychoneuroses, obesity, and in spastic conditions of the gastrointestinal tract they believe is controversial. In view of the positive danger of habituation and other untoward effects, they warn against its indiscriminate use.

An antagonistic action between amphetamine and bulbo-capnine is shown by Spiegel (176) in experiments upon rats and cats in which amphetamine abolished the catalepsy characteristic of bulbo-capnine.

The neuropathology of amphetamine poisoning was studied by Schube & Raskin (177) in guinea pigs and rats. Rather large doses were used, 0.06 to 100 mg. in acute and chronic experiments. Necropsy findings were vascular changes, stasis, congestion, dilatation of the blood vessels, and hemorrhages in the ventricles, subarachnoid space, the choroid plexus, and the meninges. There were no cellular changes in the central nervous system.

A possible mechanism for the action of amphetamine is indicated in the experiments of Mann & Quastel (178). These authors found that tyramine, isoamylamine, and other chemically related amines inhibit the oxidation of glucose by brain tissue. The inhibition is shown to be due to the formation of an oxidation product of the amine, an aldehyde. Amphetamine appears to compete reversibly with tyramine and related amines for amine oxidase whereby it reduces the rate of aldehyde formation and in this manner neutralizes the inhibiting action of tyramine. It is suggested



that the antagonistic action of amphetamine and tyramine may explain its stimulating action on the central nervous system and its beneficial effect in narcolepsy. Further research on the possible accumulation of aldehydes in narcolepsy and the role of amine metabolism therein is needed.

Beyer showed that amphetamine had a long-continued action on metabolism (179). To account for this persistence of action Beyer & Skinner (180) studied the excretion and detoxication of this drug. With the aid of a diazotization colorimetric reaction which they developed they were able to show that less than half of the ingested dose is excreted in the urine in twenty-four hours. Since absorption from the gastrointestinal canal is complete, and hydrolysis of the urine gave no higher values for the drug and since amine oxidase did not activate the oxidative deamination of amphetamine (181), and carbon tetrachloride liver injury resulted in the complete elimination of benzedrine in the urine, they tentatively concluded that the drug is slowly inactivated by loosely combining with some detoxifying substance, or that it is partially destroyed or slowly excreted in a free or a loosely combined form.

#### ALCOHOL

In a study of the mechanism of alcohol tolerance Newman & Lehman (182) found a greater degree of neuromuscular coordination in tolerant dogs at an equal blood alcohol concentration than before habituation, from which they conclude that acquired tolerance to alcohol is a tissue tolerance. The degree of acquired tolerance in dogs varies and tends to increase with habituation and decrease with abstinence (183). The postabsorptive blood alcohol curve is not affected by habituation in rabbits (184).

Studies on sugar tolerance in human chronic alcoholics were reported indicating a decrease, possibly due to undernutrition (185). Subnormal values for plasma vitamin C in chronic alcoholics (186) are in like manner attributed to nutritional defects (187). A further cause for nutritional disorders in chronic alcoholism is the reduced volume of gastric juice, diminished acidity, and a high incidence of achlorhydria (188).

Observations on the beneficial effects of thiamin in alcoholic polyneuritis were reported by Goodhart & Joliffe (189), and Bickel reported equally good effects in cardiac disorders associated with chronic alcoholism (190).



## CONCLUSIONS

Much work has been done in an attempt to find a suitable substitute for morphine, but this failed to produce practical results, though it has added considerable information to our knowledge of the relation of chemical constitution to pharmacologic action. There is as yet no substance in this group with sedative or analgesic properties which is not in some measure associated with habit formation or addiction. The renewed efforts towards a better understanding of the fate of morphine in the body promise to bear fruit in the solution of the problem of tolerance, and the recognition and emphasis of the cholinergic action of morphine may yield better methods for the prevention and treatment of opium addiction.



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